STUDY OF THYROID CANCER AND OTHER THYROID DISEASE IN UKRAINE FOLLOWING THE CHERNOBYL ACCIDENT

MANUAL OF OPERATIONS

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CONTENTS

1. INTRODUCTION TO THE STUDY

This chapter presents an introduction to the Study of Thyroid Cancer and Other Thyroid Disease in Ukraine Following the Chernobyl Accident. It includes an overview of the study design, background information, objectives and a discussion of the purpose and organization of this document, the Manual of Operations.

1.1 OVERVIEW OF THE STUDY

The nuclear power plant accident at Chernobyl released large quantities of Iodine-131 and other radioisotopes of iodine into the atmosphere, contaminating thousands of square kilometers and exposing millions of people. For this study, a well-defined subset of Ukrainian children aged 0-18 years or in utero (born after 04.26.86 and before 01.31.87) at the time of the accident will be identified and will be examined by well-trained specialists for thyroid disease annually for up to 30 years. The study is a collaborative effort of researchers in Ukraine and the United States.

The cohort will include approximately 50,000 persons who were children in 1986, all or most of whom had their thyroids measured for radioactivity during the weeks immediately following the accident (or whose mothers had measurements taken while the child was in utero). Under a rigid research protocol these subjects will receive diagnostic thyroid examinations, including palpation, ultrasound scanning, thyroid hormone and other laboratory tests, and fine-needle aspiration biopsy. Interview information regarding residential, health, diet and lifestyle history will also be collected. All subjects will be followed for thyroid cancer morbidity and mortality. Thyroid cancers will be confirmed by expert pathology examination of tissue.

In addition to the analysis of thyroid radiation measurements in May-June, 1986, efforts will be made to reconstruct each subject's exposure and to estimate the radiation dose to the thyroid. This will involve the reconstruction of deposition patterns and environmental pathways of the radioiodines, and the location, dietary characteristics, and lifestyle of each person throughout the exposure period. The procedures used to estimate dose to the thyroid are not part of this manual.

An overview of data collection activities for the study is shown in the flowchart in Figure 1.

1.2 BACKGROUND

There is ample evidence that external radiation is associated with thyroid cancer, and a number of reliable epidemiological studies show that the risk is appreciable and that the thyroid gland is one of the more sensitive human tissues (Shor 1992). Moreover, the magnitude of risk is related to age at irradiation, and is higher for children than for adults. Thus, for subjects irradiated under the age of 20 years, the (weighted mean) absolute risk is 2.6 excess cancers per 10,000 persons yr^{-1} Gy^{-1}. Available data are consistent with a linear dose response curve over much of the exposure range, although cell killing may flatten such curves at very high doses. It is noteworthy that risk of thyroid cancer has been associated with external radiation doses as low as 0.09 Gy (Ron et al., 1989).

The thyroid gland is potentially at risk in the presence of radioactive fallout. This is due in part to its ability both to concentrate iodide by a factor of about 10,000 above ambient iodide concentrations and to incorporate iodide into thyroglobulin, which has a slow turnover rate. As a result, the effective half life of iodine isotopes (except ^{129}I) is nearly as long as the physical half life.

There has been considerable interest in the nodule and cancer risk associated with internal irradiation from iodine isotopes (chiefly ^{131}I, half life of 8.05 days). The most reliable data, with good statistical power, derive from long-term follow-up studies of patients receiving diagnostic or therapeutic doses of ^{131}I. No significant excess thyroid cancer was observed in these studies of mainly adult patients. It is uncertain to what extent these results are influenced by the possibility of preexisting thyroid disease for which these procedures were carried out. In two large studies of subjects treated for hyperthyroidism with mean doses of 88-113 Gy, similarly, there was no increase in risk for thyroid cancer. Estimation of the risk of thyroid disease, including cancer, resulting from exposure to ^{131}I contained in fallout from atmospheric nuclear weapons tests is much more complicated, primarily because the radiation dose to the thyroid must be reconstructed.

There have been two studies of health effects resulting from exposure to fallout from atmospheric nuclear weapons tests. Both of these studies have used dose reconstruction techniques such as those referred to above. In a study of children living (at the time of the tests) in Utah downwind from the Nevada Test Site, the small excess of thyroid cancers was not statistically significant (Kerber et al.. 1993). The absolute risk of persons in the Marshall Islands exposed to fallout was 1.1 and 1.3 per 10,000 subjects yr^{-1} Gy^{-1} for children irradiated under 18 years of age or for adults, respectively. Six excess cancers were observed in children during the first 35 years after the fallout occurred (Robbins and Adams, 1989)

Attempts have been made to explain the remarkable difference in the rates of thyroid-cancer induction caused by external and internal irradiation. Dose rate is considered to play a major role: most data

on external irradiation were obtained from acute doses. In studies where divided doses were given the risk appeared to be decidedly smaller (Shore 1992). It has been suggested that the intermediate risk of thyroid cancer for the Marshall Island population reflects the fact that about 80% of the dose is derived from the short-lived isotopes (^{132}I, ^{133}I and ^{135}I; and <10% external) with about 15% from ^{131}I (Lessard et al.. 1985). By contrast the diagnostic and therapeutic use of ^{131}I implies a rather low dose rate. Whether the apparently low Effectiveness Factor (EF) for ^{131}I has other causes is not clear at present and animal studies are inconclusive.

In addition to thyroid nodule and thyroid cancer, external radiation of the head and neck can also result in a variety of other tumors (Schneider et al.. 1985) including parathyroid adenomas and hyperparathyroidism (Cohen et al.. 1985). Because of their proximity to the thyroid gland, the parathyroid glands may also be at risk from exposure to radioiodines, as have been shown in experimental animals (Wynford-Thomas V. et al.. 1982) and possibly in children who had received therapeutic ^{131}I for Graives Disease (Esselstyn et al .. 1982.)

The accident at Unit 4 of the Chernobyl nuclear power plant, which occurred in April 1986, was the most severe in the nuclear industry. The accident caused the death of 31 power plant employees and firemen from acute radiation exposures and burns, and resulted in the contamination of vast territories of Ukraine, Belarus and Russia. Radioactive materials were released into the atmosphere during a period of ten days. The radionuclides that are responsible for most of the radiation doses received by members of the public are ^{131}I, ^{134}Cs, and ^{137}Cs. The ^{131}I and some shorter-lived radioisotopes of iodine caused high thyroid exposures, especially among children, during the first few weeks following the accident. The longer-lived ^{134}Cs, and, more importantly, ^{137}Cs, deliver doses to the entire body and will be present in the environment for decades to come. An increase in thyroid cancer in children was reported by Kazakov et al., in 1992.

The Chernobyl power plant is located in Kiev oblast of Ukraine. A fraction of the radioactive material present in the radioactive cloud was deposited on the ground, essentially as a result of scavenging by precipitation. The contamination of the ground resulted, in turn, in the contamination of milk and other foodstuffs.

Since the Chernobyl accident in 1986 the staff of the Institute of Endocrinology and Metabolism, examined tens of thousands of children in heavily contaminated areas of Ukraine. The examinations have routinely included ultrasonography and extensive laboratory tests. Preliminary evidence is currently available which links the Chernobyl accident with a subsequent increase in thyroid cancer among children. By 1st of January 1997 923 patients with thyroid cancer who were aged 0-18 at the time of Chornobyl accident have been operated (604 of them were 0-14 years at the time of accident).

The present study builds on that experience within an epidemiologic framework calculated to create dose-specific information on the risk of thyroid disease following exposure to ^{131}I. A cohort of approximately 50,000 exposed children will be identified and examined annually for thyroid abnormalities for a period of 20 to 30 years.

1.3 OBJECTIVES

This collaborative investigation possesses both scientific and public health objectives. The scientific objective of the study will be to provide new knowledge on the correlation of thyroid diseases with radiation dose. The aim of the study will be to carry out valid and credible assessments of the early and late morphologic and functional changes in the thyroid glands of persons exposed to radiation from radioactive materials released as a consequence of the Chernobyl nuclear power plant accident. The emphasis is on dose-and time-specific changes, including but not limited to the following specific topics:

- Risk estimates, as a function of dose, for morphologic changes (i.e., nodules and cancer) in relation both to sex and to age in 1986; comparison of the relative effectiveness of ^{131}I with that of published x-ray and gamma irradiation in inducing thyroid nodules and cancer.
- Risk estimates, as a function of dose, for induction of hypothyroidism and autoimmune thyroiditis in relation both to sex and to age in 1986.

In the course of the study other possible risk factors will be examined including dietary iodine intake during and after 1986, and the ingestion of potassium iodide for thyroid protection shortly after the accident.

The intended study also possesses practical public health objectives and implications. Most importantly, the study will provide guidance for the mitigation of the effects of the Chernobyl accident on thyroid disease in those exposed as children. It may also provide the basis for a radiation protection policy with respect to thyroid disease, not only in Ukraine but wherever nuclear power plants exist. The administrative implementation of the study will enhance the training and experience of younger specialists, not only in endocrinology and ultrasonography, but also in modern research methods appropriate for clinical follow-up studies, clinical trials of therapy, and case-control studies.

Finally, the establishment of a large fixed cohort and associated database on children and their parents will make available an asset that can be used for many other studies of the effects of the Chernobyl accident.

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2. PURPOSE AND ORGANIZATION OF THE MANUAL OF OPERATIONS

The purpose of this manual is to provide documentation of all study procedures except dosimetry. It is expected that this manual will be used as a resource by all members of the study team. The manual will be updated to reflect changes in procedures over the course of the study, all changes to be dated and certified by both UA and US representatives. The English and Russian versions must be in agreement. The Director is responsible for ensuring that updates are distributed to all holders of the manual.

The manual has been structured so that sections dealing with procedures for a particular task can be readily identified and can be provided to the individual involved in that particular task.

Descriptions of study procedures are given in Chapters 3-8 of the manual. Chapter 9 presents an overview of data management activities. The appendices which follow Chapter 9 contain the data collection forms and instructions for their use and samples of other study materials such as contact letters, logs and management forms and reports.

3. DEFINITION OF STUDY COHORT

In order for subjects to be included in the study cohort they must fulfill certain eligibility criteria. These criteria are detailed below.

3.1.1 ELIGIBILITY CRITERIA

The eligibility criteria are as follows:

1. The subject must have had direct radiation measurement of the thyroid in 1986 according to the file maintained in the Research Center of Radiation Medicine. For the in utero exposed, it is the measurement of the mother's thyroid that determines eligibility.
2. The subject's date of birth must fall in the interval 26 April, 1968, through 31 January, 1987.
3. The subject must be a resident of Ukraine at the start of the study.

3.1.2 POSSIBLE REASONS FOR EXCLUSION

There are no medical exclusion criteria for the study, including thyroid diagnoses already made.

The dosimetry group will use its judgment in omitting from the sample selection children with radiation measurements that are known to be useless.

It should be noted that following initial sample selection, loss to follow-up will occur for a variety of reasons including:

- subjects who cannot be identified or located
- subjects who emigrate from Ukraine
- subjects who are too ill to participate
- subjects with physical or mental impairment which precludes participation
- subjects who moved from the catchment area

Subjects initially selected will always remain part of the cohort. Reason for subject non-participation will be documented in the study management system (see Chapter 9).

3.2 SELECTION OF THE COHORT

3.2.1 INITIAL STEPS

The dosimetry group of the Research Center of Radiation Medicine will provide a copy of the measurement file for children 0-18 in 1986 (see the research protocol, Section 3.2, Table 3.2.1) from which the epidemiology group and the data coordinating center will make the initial selection on the basis of the estimated dose, residence at exposure, and apparent adequacy of information. All decisions made during sample selection will be carefully and completely documented.

Although the protocol call for an 'intensive sample ' of 50,000, the expectation is that a manageable cohort will be smaller, perhaps in the range of 30,000-40,000. Accordingly, an initial selection (Selection 1) of about 20,000 will be made, as follows:

1 or more Gy	all 9,800 available
0.3 - .9 Gy	5,000 from the 18,500 available
<0.3 Gy	5,000 from the 46,100 available

Selection from the two lower dose groups is to be made at random from the file. Subsequent selections will be made when the desired cohort size becomes fixed.

Additional details of the sample selection are provided in Appendix K.

3.2.2 THE IN UTERO GROUP

Since the measurements file will contain no direct measurements on the in utero exposed, their selection will depend on the availability of maternal measurements. Dosimetry Registry of Research Center of Radiation Medicine transfer information they have pregnant women to epidemiology group and DCC. The epidemiology group will examine birth records and/or hospital records from the obstetric hospitals which serve the catchment area for births in the interval 26 April, 1986 and 31 January, 1987, abstract names and addresses of parents, and provide the list to the dosimetry group for record linkage to identify in utero exposed with maternal measurements.

3.3 ASSIGNMENT OF STUDY IDENTIFICATION (ID). NUMBERS AND SPECIMEN IDENTIFICATION NUMBERS

Study identification (ID) numbers will be assigned to each study subject after the initial selection has been made from the dosimetry file (without regard for any subsequent events that may result in non-participation). The file of selected study subjects will be sorted in random order before subject ID assignment to avoid having the subject's ID number indicate his probable dose range. After the random sort, the ID numbers will be assigned sequentially.

The ID number will consist of 8 digits: 6 for the individual's unique number, and 2 for the check number. The check number will be assigned as the sum of the 6 digits in the unique number.

The ID number will be used to identify the individual subject on all data associated with that subject. No ID number, once assigned, can be reassigned to another participant, changed or deleted. If the subject becomes ineligible after the ID has been assigned, the ID will **not** be reassigned. This policy ensures that data associated with a subject will not be lost or inadvertently attributed to another subject.

In addition to the subject ID number, separate, unique specimen ID numbers will be used. These numbers will be assigned to the blood samples collected from the study subjects each year, and the urine samples collected on a subsample of the study population in the baseline year. The link between the subject and his specimens will be made through these specimen ID numbers which will be placed on the blood and urine collection forms (along with the subject ID) and keyed into the study computer system. Blocks of specimen ID numbers will be assigned by the data coordinating center for each calendar year. The structure of the specimen ID number is: 1st 2 digits=calendar year, 3rd-8th digit=sequential number. In the end of ID number will be added a letter, appropriate to the type of the sample ('K' for the blood samples, 'M' for the urine samples, for example: 97000001K).

ID labels will be generated for both subject ID and specimen ID numbers which can be applied to the forms and specimen collection and storage containers. These will be provided by the data coordinating center. Two types of subject ID labels may be generated. The first type may contain the subject ID number

only, and the second may contain the subject's ID along with other identifiers such as name and date of birth.

Specimen ID labels will contain numeric information only, and may be used to identify the facility at which the screening took place.

3.4 ABSTRACTING RECORDS BEFORE INITIAL CONTACT

Preliminary demographic and identifying information will be collected on each subject selected for the cohort, mainly to provide information which will be useful in making contact with study subjects. It is expected that computer sources will mainly be consulted to obtain this information. The specific items of information to be collected are:

- Full names of subject, parents, as well as other family members or providers
- Date of birth of subject
- Address on 26 April, 1986
- Date of and location where the thyroid was measured
- Addresses subsequent to 26 April 1986, with dates
- The documentation of any information pertaining to thyroid disease that may be seen in any of the record sources, with identification of the condition and of the source, and of any applicable date of the condition, such as date of diagnosis.

This information will be recorded on the **Initial Abstract Form** and entered directly into a computer file or loaded onto the study computer from other files. Organizational responsibility for this work will be assumed by the Epidemiology Group and the data coordinating center. The Initial Abstract Form and instructions for its use are listed in Appendix A-3-1.

Sources from which the above information will be obtained may include:

- Database of clinic in Institute of Endocrinology & Metabolism
- Files of Ukrainian Center of Informational Technologies and National Registry Ministry of Public Health of Ukraine (Chornobyl Registry)
- Paper files of rayon polyclinics
- Local rural and urban authorities (selsky sovet, etc)
- Special departments of different ministries (military, internal affairs, public education)

It is not expected that **all** sources will be consulted for all subjects. Initially, information will be sought by linking any available computer files, most notably the national registry of Chernobyl victims and other files of the Research Center of Radiation Medicine. The material taken from these various files will be edited for consistency.

3.5 OBTAINING CURRENT ADDRESSES

Before allocations can be made to the individual examining teams by the data coordinating center, at least some addresses will have to be obtained. The effort to obtain addresses will be a continuing and intensive effort by the epidemiology group and the data coordinating center for the first three years of the study. Subsequent steps will include:

- record linkage with all available computer files;
- available paper files of the Institute of Endocrinology .
- files of appropriate ministries;
- urban and rural authorities of localities where subjects lived on 26 April 1986; and mailings to verify addresses.

3.6 ALLOCATION OF SUBSAMPLES TO EXAMINING UNITS

The examinations will be performed principally in one fixed center, and in the field by three mobile teams. When a sufficient number of subjects has been located, a tentative map will be prepared to define the geographic boundaries of the areas of responsibility for the examining units. Ideally these boundaries should be mutually exclusive. In the aggregate they constitute the catchment area.

It is to be expected that, over time, as the study matures, there will be changes in the precise boundaries of the areas served by the examining units, as well as in the assignment of subjects to particular examining units. There will be subjects who initially reside outside the geographic boundaries of catchment area. However, in subsequent years, as boundaries change, or members of the cohort move into the catchment area, they should be included into the screening process. It is important, therefore, that all members of cohort be tracked and contact be maintained.

3.7 SUPPLEMENTATION OF THE INITIAL LISTING

If, during the first three years, sample losses from refusal, emigration, and failure to locate, appear to require it, consideration will be given to a re-selection of potential subjects from the file of measurements and/or selection of subjects with only passport doses. The re-selection will employ the same principles as

governed the initial selection and will be reviewed by the study advisory group to ensure that sound scientific principles are applied.

4. CONTACT PROCEDURES

4.1 PUBLICITY

Before contact is made with individual families, the Ministry will mount a publicity campaign in the mass media and through medical channels. Local and central newspapers, radio, and television will all be employed to explain the purpose and the content of the study. The publicity will stress the value of the study to the health maintenance of the individual. The schedule for publicity will need to be carefully timed given that there will be somewhat of a gradual start to the study. Material may need to be repeated throughout the first year of the study and beyond as deemed appropriate.

4.2 INITIAL CONTACT WITH STUDY SUBJECTS

The data coordinating center and epidemiology group will take the leading role in initial contact with study subjects and their parents. It will be important for a parent to accompany the study subject to the first visit in order to provide the most accurate information needed for dose reconstruction. The family (or adult subject) will first receive a letter from the deputy Minister of Health describing the study and its benefits to the individual, specifying the place of examination and an appointment time and date or a range of dates with information on how to arrange and confirm appointments by postcard and telephone. This letter will be sent out by the data coordinating center. With the letter will be a pre-printed, stamped card to be mailed back to the epidemiology group. It will provide for confirmation of the offered appointment, a request for an alternative or deferred appointment, and a telephone number (if available) where the subject and his parents may be reached. As this cards came to the epidemiology group, sorted out, Initial Abstract Form filled out, Data coordination center will make Registration Log and will forward it to the fixed or Mobil team. If the subject and accompanying parent do not appear for the scheduled appointment, the fixed or mobile team will inform the data coordinating center, they will inform epidemiology group, which will follow-up this contact and conduct any further scheduling activities. Copies of the letter and appointment confirmation card are in Appendix C-4-1.

4.2.1 HANDLING NON-RESPONSE

There are three major categories of non-response. The first is inability to locate the subject. This may result from having an incorrect address in the study records, from having an old address (the subject has moved) or having no address at all. The second major category is inability to contact the subject. Attempts to reach the subject, either by mail or by phone, may be unsuccessful. The third category is refusal. Subjects (or their parents) may be reluctant to participate due to a misunderstanding of study objectives, a negative attitude toward medical examinations or other reasons.

The data coordinating center will be responsible for informing the epidemiology group of non-response subjects who require follow-up. The epidemiology group will be responsible for coordinating appropriate follow-up activities and reporting on them to the data coordinating center. Some initial steps such as sending a second letter, attempting a telephone contact or sending a registered letter will be carried out by the data coordinating center. Support from local medical authorities at the raion level will be sought for locating, contacting and convincing reluctant subjects to participate. This support will be officially requested from the Minister of Health.

For subjects who cannot be located or contacted, lists will be sent to the local medical authorities at the raion level to request their assistance in locating the subjects. For refusals, the epidemiology group will provide the local medical authorities with the reasons for refusal and request that they contact the subjects in the attempt to involve them in the study. It is felt that this approach may be effective since local medical personnel are more familiar with specific issues in their region and are psychologically closer to the inhabitants of the individual raion. It is also possible, due to closer proximity, that local medical personnel may be able to discuss the study with the subject, **in-person**. Such direct contact may result in better communication and therefore more success in convincing reluctant subjects to participate.

Other possible tracing sources include databases which cover large segments of the population. The epidemiology group and the data coordinating center will be on the lookout for appropriate databases suitable for record linkage by computer. The Chernobyl Registry is an example.

4.3 OBTAINING INFORMED CONSENT

Informed consent (or assent) will be obtained through a written informed consent statement (Appendix B-5-1) which will be read to or by the parents of children or to adult subjects. The subject or parent will then be given an opportunity to ask any questions. No signatures will be required of the parent, child or adult subject but the staff person who administers the form will note, and initial, the fact of acceptance or refusal. Informed consent will be obtained during the initial clinic visit as described in Section 5.1.

4.4 SCHEDULING SUBJECTS FOR EXAMINATION

The study eventually plans to provide examinations for perhaps 30,000 - 40,000 children and adult subjects (final number to be determined), and for examinations to be repeated at yearly intervals. During the first full twelve months of the study, after pilot work has been performed, it is expected that perhaps subjects will be examined, in the second year, and about in the third year.

4.4.1 INDIVIDUAL APPOINTMENTS

The fixed or mobile team and the data coordinating center will agree on an anticipated flow of subjects for examination over a fixed period of time. The data coordinating center will make a selection of subjects, send the initial letter from the deputy Minister of Health with the information about appointment. The epidemiology group center will then be responsible for appointment confirmation and Data coordination center will take care about re-scheduling. Names and other identifying information, and dates of confirmed appointments, will be provided by the data coordinating center to the fixed team over the computer network.

Appointment making for a mobile unit will be handled by the data coordinating center in the same manner as making appointments for fixed team visits. The data coordinating center and epidemiology group will similarly be responsible for appointment confirmation and re-scheduling.

The data coordinating center may also carry out some initial follow-up activities with non-responders such as sending a second letter, or making a phone contact. Those who do not respond to these efforts will be referred to the epidemiology group for further follow-up (see Section 4.2.1).

For appointments made more than a month in advance, subjects will be sent a reminder notice from the data coordinating center a few days before the scheduled appointment. Subjects may also be called the day before to confirm the appointment and answer any questions, if it is known that the subject can be reached by telephone

4.4.2 CONTROLLING THE FLOW OF SUBJECTS TO EXAMINING CENTERS

The data coordinating center will maintain a record of appointments made for each subject, dates of examinations, and will re-schedule subjects for examination yearly on the basis of the capacity of the fixed or mobile team. Every effort will be made to schedule annual examinations within plus or minus one month of the date of the subject's baseline examination. This time period is referred to as the visit "window."

4.5 MAINTAINING CONTACT WITH MEMBERS OF THE STUDY COHORT

At the initial screening visit, the subject will be asked to provide information which will help locate him in the future. This information will be recorded onto the **Locator Form**. The form and its specifications appear in Appendix B-5-2. Items of information on this form include complete name of subject and parents, present address and telephone number, complete date of birth, indication of any plans to move, the names and addresses of two close relatives or friends who do not live in the subject's household but would know his whereabouts and the name of the subject's home polyclinic. The Locator Form will be reviewed with the subject and updated as necessary at each annual clinic visit.

The data coordinating center will be responsible for informing epidemiology group of non response subjects who require follow up tracking efforts, epidemiology group will be responsible for follow-up activities and reporting their results to the DCC. Some initial steps, such as sending second letter, a second telephone contact, or sending a registered letter may be carried out by the coordinating center or by the supporting facility in the field. Support from local medical authorities at the highest level will be sought for locating, contacting and convincing reluctant subjects to participate. This support will be officially requested from the ministry of Health.

Other possible tracing sources include data bases that cover large segments of the population. The epidemiology group and the DCC will look out for appropriate data bases for record linkage by the computer. The Chernobyl Registry is an example, especially since it is continuously updated.

4.6 DOCUMENTING PARTICIPANT STATUS

The status of each study subject will be tracked through the study computer system. Information will be entered to indicate whether the subject is an active participant, has refused, is lost to follow-up, or has moved outside Ukraine. The participant's status in terms of completion of data collection activities will also be maintained in the system. Documents describing reasons for refusal or steps taken to trace a lost subject will also be used and will be filed with the data coordinating center (see Chapter 9). The data coordinating center will provide the examining groups, as well as the epidemiology group with monthly or quarterly reports on patient participation.

4.7 HANDLING OF INDIVIDUALS WHO ARE NOT COHORT MEMBERS BUT WISH TO BE EXAMINED UNDER THE RESEARCH PROTOCOL

If a person approaches a fixed or mobile team for examination and time is available, he may be offered palpation and ultrasound examination of the thyroid. However, blood would not be drawn and a written result would not be made. In the case of an abnormal finding, he would be referred to a polyclinic or hospital, as appropriate.

5. EXAMINATION PROCEDURES

The examinations will be performed in fixed center and by mobile teams. There will be one fixed team in the Institute of the Endocrinology and Metabolism end 3 mobile teams. The subject will ordinarily arrive with his appointment card in hand. He is to be welcomed and thanked for coming. The subject will be directed through the various examination stations where he will be interviewed, provide a blood sample and a urine sample (baseline year only) and have the thyroid ultrasound and thyroid palpation examinations. At the end of the examination process the subject will receive the Preliminary Summary of Medical Findings and Recommendations (next visit in a year, check-up in six months, referral to hospital, etc). A copy of this summary will remain in the subject's chart.

5.1 REGISTRATION AND INFORMED CONSENT

When the subject enters the examining area, he will be greeted by the registration nurse, who will carry out registration activities. The arrival of the subject will be documented in the Registration Log (Appendix B-5-1). The Registration Log will have been prepared in advance (printed with the identification numbers, names and dates of birth of scheduled subjects) by the data coordinating center. Mobile team will receive Registration Log from DCC before their trip.

If this is the first visit, the subject's identifying characteristics (full name, full date of birth, present address and telephone number if available, and parental names) and name of home polyclinic will be obtained/verified. This information will be recorded on the **Locator Form** (see also Section 4.5). Other information recorded on the Locator Form includes an indication of any plans to move and the names and addresses of two close relatives or friends who do not live in the subject's household but would know his whereabouts. This form will be administered by the registrar. At each annual visit, the information on this form will be reviewed and updated, as necessary. The Locator Form and its specifications are in Appendix B-5-2. At the first visit, the informed consent statement will be read to or read by the subject or an accompanying parent.

If the subject is under 16 years of age, oral parental consent to the examination will be sought from an accompanying parent and the assent form will be read to the subject. If the subject is 16 or older, consent will be sought from the subject directly. Informed consent will be obtained once for the entire study and need not be obtained again during subsequent examinations. The informed consent statement is shown in Appendix B-5-1. (The consent may be administered by the interviewer at the interview station. It is important that it be administered before any data collection activities are initiated.)

The subject's envelope will contain all necessary labels for the study forms (except for specimen labels) and the study **Control Form**. At each examining station, the study personnel will remove a label from the subject's envelope, label and complete the study form, and return the form to the subjects envelope. Specimen labels for the Blood and Urine collection forms, as well as for specimen containers will be attached at the specimen collection and processing stations. The envelope will also contain the Control Form. The Control Form will reflect whether or not the subject is required to complete the urine collection procedure. Urine collection will only be required if the subject was pre-selected for urine collection (see Section 5.2.2) Information will also be recorded on this form by the examiner at each examination station to indicate whether the particular exam component was completed. The Control Form and instructions for its use appear in Appendix B-5-4. After receiving the envelope, the subject will be directed or taken to the first examining station where interviewing takes place.

5.2 SEQUENCE OF EXAMINING STATIONS AND PATIENT FLOW

The usual sequence. especially in a fixed examining center will be as follows:

- Interview
- Urine collection
- Blood collection
- Clinical examination and thyroid palpation
- Thyroid ultrasound

The sequence of urine and blood collection may be varied by mobile teams. However, the ultrasound/thyroid palpation order will always be maintained. The subject first will be seen by the ultrasonographer who will, however, perform thyroid palpation before the ultrasound examination (see Section 5.2.4). If the patients flow is big, subject might be seen first by the endocrinologist and then by the ultrasound specialist.

After the examination endocrinologist will fill out Preliminary Summary of Medical Findings and Recommendations.

5.2.1 INTERVIEW

Interview forms and content differ for first vs subsequent visits. The interviewer will welcome the subject and the accompanying parent and explain the purpose of the interview and its content, relating it to health maintenance as much as possible. The interviewer will remove the labeled interview form from the package brought by the subject and proceed with the interview. The interviewer will enter the replies to the questions asked on the form and will print and sign his name on the completed form. Before releasing the subject the interviewer will scan the form for any gaps or inconsistencies that might be corrected before the subject leaves the station. At the conclusion of the interview the subject and the accompanying parent will be asked if there are any questions that the interviewer might answer. If medical questions are asked, they will be advised to take them up with the endocrinologist after the thyroid examinations.

The **Initial Interview Form** is shown in Appendix A-5-1. Specifications for administration of this questionnaire are also included in this Appendix. The **Annual Interview Form** used in subsequent years of the study is in Appendix A-5-2 along with instructions for its administration. General interviewing techniques are provided in Appendix D. These techniques provide the fundamental principles with which interviews should be administered in the epidemiologic research setting. All interviewers will receive training on general interviewing techniques and on the interview forms before they begin administering the questionnaires.

Depending on the age of the child, the questions asked and period of time to be remembered, one of the parents can be considered as the most appropriate person to be interviewed. It should be clarified before the interview.

The Control Form will be marked to show that the interview was completed. The subject will be thanked for his contribution and directed to the next examining station. This may be for urine collection or for blood drawing.

The completed interview form will be placed in the collection box at the interview station pending pick-up by the data entry specialist.

5.2.2 URINE COLLECTION AND POST-COLLECTION PROCEDURES AT THE EXAMINING LOCATION

The protocol for urine collection calls for collection of urine only in the baseline year and only on a sample of subjects representing specific raions with the objective of collecting 80-100 samples per raion.

Subjects selected for urine collection will be pre-designated by the data coordinating center. The examining center will receive a list of subjects selected for urine collection. The requirement to complete the urine collection procedures will be reflected on the subject's Control Form.

5.2.2.1 RATIONALE

Estimation of the content of the iodine in urine will help to characterize the existing iodine deficiency, there spreading and grade in the examining regions of Ukraine.

5.2.2.2 EQUIPMENT AND SUPPLIES

Supplies needed for the urine collection include:

- Urine collection containers with lids
- Urine Collection and Processing Form
- Specimen ID labels

Supplies needed for processing urine samples at the examining center include:

- Urine transport tube with cap, 2 per person
  (CMS Catalog, p. I-338)
  (NOTE: A falcon tube with conical bottom may be preferable because the tubes can be placed easily into a Styrofoam rack for storage and shipment.)
- Rubber gloves
- Disposable pipets
- Urine Collection and Processing Form
- Specimen ID labels

Supplies needed for local storage and shipment of urine samples include:

- Storage boxes (or racks)
- Plastic bags
- Shipping boxes
- Transmittal Form

5.2.2.3 TRAINING AND CERTIFICATION OF PERSONNEL

Collection and processing of the urine will be handled by the nurse-assistant. Training on processing, storage and shipping procedures will be conducted by staff of the Central Laboratory. No certification of personnel will be required.

5.2.2.4 INSTRUCTIONS FOR URINE COLLECTION

Urine collection will be administered by the nurse assistant. He will first determine the eligibility of the subject for the collection. This will involve questioning the subject about current thyroid hormone medication

usage. Urine samples will not be collected from persons taking thyroid hormones. If eligible, he will label the Urine Collection and Processing Form with one of the attached specimen ID labels and proceed to ask the subject about polyvitamin and other medication usage and record this information on the form (see Section 5.2.2.7).

The nurse-assistant will label the collection container with the specimen ID and instruct the subject to empty his bladder into the container. After producing the sample, the subject should replace the lid on the container and return it immediately to the nurse assistant. The nurse assistant will record the date and time of collection onto the Urine Collection and Processing Form and the fact of collection on the Control Form before sending the subject to the next station. It is very important that only provided containers be used - others might have contamination, i.e., a sample collected by the subject at home in his/her own container should not be used. Any sample with known iodine contamination should be marked and kept separate from uncontaminated samples.

5.2.2.5 INSTRUCTIONS FOR URINE PROCESSING

The urine sample will be accompanied to the urine processing station by a Urine Collection and Processing Form and additional specimen ID labels. (it is noted that the processing station may be in the same workspace as where collection was handled.) Processing of the sample should be done as soon as possible after collection. Urine samples collected by mobile unites should be refrigerated and tested preferable within a week, otherwise, a drop of sodium hydroxide will be added as a preservative.

Processing steps include preparation of two aliquots of 5 ml each. The two 5 ml transport tubes should be labeled with specimen ID labels and 5 ml of urine transferred by pipet into each tube. The remainder of the urine sample will be discarded. The time of transfer will be recorded on the Urine Collection and Processing Form.

5.2.2.6 INSTRUCTIONS FOR STORAGE AND SHIPMENT OF URINE SAMPLES

The urine aliquots will be placed into a storage box and stored under refrigeration (4^{0} C.) until shipment to the Central Laboratory. Alternatively, the samples may be stored in racks. Shipments to the Central Laboratory will be made on a weekly basis. For shipment, the samples will be placed into a large shipping box, appropriately labeled. If stored in racks, each filled rack should be placed into a plastic bag first. A transmittal form will accompany each shipment. The transmittal will list the date and contents of the shipment i.e., a listing of all specimen ID's included in the shipment. A copy of the transmittal will be kept at the local facility and another copy will be sent to the data coordinating center.

5.2.2.7 DATA COLLECTION AND TRANSFER TO DATA CENTER

Information regarding urine collection and processing will be documented on the **Urine Collection and Processing Form**. The form will be pre-labeled with the subject ID number and have a set of specimen labels attached to it. After determining that the subject is eligible for the urine collection (i.e., not taking thyroid hormone medication), the nurse assistant will affix a specimen ID label onto the form and will record the polyvitamin, and medication information, the date and time of collection and any problems with the sample. The nurse assistant will then document the preparation of the two aliquots of 5 ml on the form. The form will be placed in the collection box for pickup by the data entry specialist. See Appendix A-5-3 for a copy of the Urine Collection and Processing Form and specifications for its completion.

If a urine sample is not collected on a subject who was pre-selected for urine collection, this fact will be recorded on the Control Form and the Urine Collection and Processing Form will not be completed. If the subject was not selected for urine collection, the urine collection box on the Control Form will be marked "not applicable."

The urine samples themselves will be shipped to the Central Laboratory accompanied by the Urine Collection and Processing Form and a transmittal form listing the date of shipment and ID numbers of all samples in the shipment (see Appendix B-5-5). Copies of the transmittals and data on diskettes will be sent to the data coordinating center. This will allow the data coordinating center to monitor the shipment of samples and track receipt of test results.

5.2.2.8 QUALITY CONTROL

Quality control for urine collection and processing will be implemented through the following steps:

- Direct observation of collection and processing procedures at the examining center by the Quality Control Officer.
- Ongoing evaluation of the number of subjects providing a urine sample. If the number is low, the reasons and possible solutions will be explored.
- Checking each lot number of transport tubes for possible iodine contamination. This will be done by the Central Laboratory who will control the supply of these tubes to the examining centers.
- Documenting the collection and reviewing any problems noted on the Urine Collection and Processing Form.
- Reviewing results from the laboratory testing to ensure that collection, processing, field storage and transport procedures are providing adequate samples for the test procedures.

- Checking the interval from collection to receipt at the Central Laboratory.

5.2.3 BLOOD COLLECTION AND POST-COLLECTION PROCEDURES AT THE EXAMINING CENTER

The same procedure as described for urine collection (see Section 5.2.2) will be followed for the blood draw. The phlebotomist will put the subject's ID label on the blood collection form, and along side it will be placed the unique specimen ID label. The remaining foil-back blood specimen labels will be placed on the aliquotted tubes. Ten ml. of blood will be collected annually into one 10 ml. serum separator vacutainer tube. The samples will be spun down to separate serum. The serum will be aliquoted into labeled cryovials, frozen to -20^{0} C., and shipped periodically to the Central Laboratory for evaluation of TSH, anti-TPO and serum calcium. Blood samples collected in mobile units will be transmitted frozen to the Central Laboratory.

5.2.3.1 RATIONALE

Assays to be performed on the blood samples will be used in the diagnosis of thyroid abnormalities (e.g., thyroid function abnormalities, autoimmune thyroiditis), parathyroid abnormalities and for the follow-up of thyroid pathology.

5.2.3.2 EQUIPMENT AND SUPPLIES

The materials and supplies needed for the blood collection are as follows:

- 10 ml serum separator tubes; 1 per person
- Vacutainer needle holder, standard size
- Tourniquet, latex
- Alcohol wipes, individually wrapped
- Sterile gauze
- Bandaids (bandage strips)
- Test tube rack
- Biohazard bags
- Disposable gloves, latex, small, medium, large
- Blood Collection and Processing Form
- Specimen ID labels

It should be noted that vacutainer tubes should be at room temperature at the time they are used. They must be protected from extremes of temperature and stored at a constant temperature in a cool place. The vacutainers are also dated. Each box of tubes has an expiration date printed on it. Expired tubes should not be used.

Supplies needed for processing the blood samples include:

- 10 ml vial 1 per subject per draw
- 1.0 ml Cryovial closure color-coders, 3 per person per draw
- blue color - for immunoferment assey, 2 per person per draw
- green color - for Ca, 1 per person per draw
- Transport tubes, 2 per subject per draw
- Disposable Pasteur-type transfer pipettes (0.1-1.00 cm)
- Cryovial holder
- Blood Collection and Processing Form
- Specimen ID labels

The supplies needed for storage and shipment of processed samples are as follows:

- storage boxes
- map cards
- box labels
- transport coolers
- Blood Collection and Processing Form
- Transmittal Form

5.2.3.3 TRAINING AND CERTIFICATION OF PERSONNEL

Blood collection will be performed by experienced and trained phlebotomists. Training in study-specific phlebotomy procedures (i.e., using vacutainers) will be carried out in a short 2-3 day course for all phlebotomists. No special certification will be required. The quality of the blood collection carried out by the phlebotomists will be evaluated through the success of their draws and the testing of the collected samples (see Section 5.2.3.9 below).

A laboratory technician will carry out the processing of the blood samples. Training and certification will be conducted by the Central Laboratory. Detailed written instructions on processing procedures will be prepared by the Central Laboratory. The laboratory technician will be required to familiarize himself with these procedures and will then perform them under the direct observation of Central Laboratory senior

personnel. After certification has been carried out, the names, dates and certification status of all laboratory technicians will be documented. This documentation will be kept on file at the data coordinating center. The data coordinating center will track the status of certification and advise the Central Laboratory when recertification is required. Recertification will be required on an annual basis.

5.2.3.4 INSTRUCTIONS FOR THE BLOOD COLLECTION

PREPARING FOR THE DRAW

Before the blood sample is drawn, the subject should be questioned about bleeding disorders; extra precautions may be required in this situation. The subject should rest in a seated or reclining position for at least 5 minutes before the draw and remain in this position during the venipuncture. Having the subject sit or recline helps guard against any injury that might result if the subject faints.

It is extremely important that the anticipated puncture site and all necessary equipment, including needles and tubes be kept absolutely sterile and free from contamination. Extreme caution must be exercised throughout the collection of blood so that the data are valid and subjects and study workers are protected. Biosafety guidelines are provided in Appendix E.

Additional preparation steps for the phlebotomist include:

- Place the venipuncture equipment where it is readily available but not in danger of being upset. Keep extra equipment within easy reach.
- Thoroughly wash your hands.
- Put on gloves.
- Prepare the blood collection tube, placing it in a test tube rack until you are ready to use it and labeling it with the appropriate specimen ID label. Labels will be attached to the subject's Blood Collection and Processing Form.

VENIPUNCTURE TECHNIQUE

- Instruct the subject to extend the arm palm up and straight at the elbow.
- Position the arm on your work table so that the veins are readily accessible and you are able to work in a comfortable position. Be sure that the arm is in a downward position with the elbow lower than the heart to prevent backflow.
- Inspect the arm to use for venipuncture. The veins of choice are those located in the antecubital area. Do not draw blood from an arm which has a rash or open sore or is swollen or edematous.
- Apply the appropriate latex strip tourniquet several inches above the subject's elbow.
- Select a vein that is palpable and well-fixed to surrounding tissue. Palpate even when the vein can be seen. If the veins do not distend rather quickly, the following techniques may be used.
- Have the subject open and close the hand several times.
- Massage the arm from wrist to elbow; this forces blood into the veins.
- Tap the area sharply with the index and second finger two or three times; this causes the veins to dilate.
- The arm to be used for venipuncture may be hung at the subject's side without a tourniquet. This will allow the veins to fill with blood to their capacity.
- Examine the subject's other arm. Sometimes the veins in one are larger than in the other.
- If the tourniquet has been applied for more than one minute while you search for a vein, release the tourniquet for two to three minutes. Prolonged obstruction of blood flow by the tourniquet is unnecessary and uncomfortable for the subject, and may alter certain results.
- Check carefully for scar tissue or the presence of tendons near the vein.
- Cleanse the area with an alcohol wipe. Hold the alcohol wipe with two fingers on one side of it, so that only the other side of the wipe touches the area of the puncture site. Cleanse the area using a circular motion beginning with a narrow radius and moving outward so as not to cross over the area already cleansed. Repeat with a second alcohol wipe. Dry the cleansed area using a sterile 2x2 gauze pad. The area should be completely dry before the venipuncture is done in order to reduce the burning sensation caused by alcohol penetrating the skin.

CONDUCTING THE VENIPUNCTURE

- Open needle package and assemble vacutainer holder and the needle by screwing threaded end of needle onto the holder.
- Place the tube to be drawn into the holder, securing it slightly, but not penetrating the stopper.
- Ask subject to make a fist.
- Remove sheath from needle.
- The vein should be "fixed" or held taut during the puncture. Place the left thumb about one inch below the point of entry and pull skin gently in a downward motion. (This stretches the skin and "anchors" or "fixes" the vein.)
- Hold the needle in line with the vein, with the bevel up and at a 15^{0} angle with the skin.

- Push the needle firmly and deliberately into the vein. As the needle enters the vein, you will notice a little "give."
- Quickly push the vacutainer tube into the holder, puncturing the stopper. Blood will be drawn into tube. If no blood enters the tube, and no bruise is forming, probe the vein until entry is indicated by blood flowing into the tube. If no blood enters the tube and a bruise is forming, release the tourniquet and remove the needle immediately. Do not keep probing for the vein as this can cause severe bruising. Place a gauze square over the puncture site and apply firm pressure to the puncture site for three minutes.
- HOLD THE TUBE IN A DOWNWARD POSITION, with the stopper uppermost.
- Release tourniquet as soon as good blood flow is achieved. (NOTE: It is important that the tourniquet be released as soon as possible. There is some evidence that leaving it on too long can affect the results of the calcium assay.)
- After the tube is filled to capacity, carefully pull it out of holder.
- Gently remove needle and holder assembly in a smooth quick motion, covering site with a sterile gauze pad.
- **Discard the needle without capping it in the needle disposal box.** When the box is full, place it into a biohazard bag along with any other contaminated waste paper.
- Immediately invert the tube 5 times, gently.
- Write the date and time of collection directly on the tube.
- Check the venipuncture site. If it is adequately clotted, apply tape over the gauze pad. Instruct the subject to remove it in no less than 45 minutes if the bleeding has stopped. Also, suggest that the subject sit quietly for a few minutes.
- If bleeding continues, keep direct pressure on the site for five minutes or more.
- Report any adverse reaction to venipuncture to a physician immediately.
- No more than 2 attempts may be made on one arm; in the event of failure with the arm of choice, the other arm may be used.
- For any vasovagal or syncopal episode, the subject will be instructed to put his head between his knees. An inhalant may be used. If the episode continues, a physician should be notified.
- Record the date and time of the blood draw and any problems onto the Blood Collection and Processing Form.
- Record the success of the blood collection onto the Control Form and direct the subject to the next station.

5.2.3.5 PROCESSING PROCEDURES IMMEDIATELY AFTER THE BLOOD DRAW

The following steps will be carried out by the phlebotomist immediately after the blood draw is complete:

- The tubes will be allowed to stand (without being moved) at room temperature (18-20^{o} C) for 30 to 45 minutes from the time of the draw. This is to allow complete clot retraction.
- The tubes will be transported to the processing station. (It is noted that the processing station may be in the same workspace as where collection was done.)

5.2.3.6 PROCESSING THE BLOOD SAMPLE

The blood sample must be centrifuged, the serum separated from the clot and the serum samples aliquoted and frozen **on the day of collection**. The following steps will be carried out by the laboratory technician:

- Centrifuge the 10 ml tube in which the sample was collected for 15 minutes at room temperature at 1200 x g.
- Inspect the serum to determine if it is hemolyzed, icteric, turbid or lipemic. These problems should be documented on the Blood Collection and Processing Form.
- Prepare 3 storage vials by labeling them with the specimen ID labels and prepare colored cups (coders) in following order: 2 blue color - for immunoferment assay, 1- green color - for Ca. Specimen ID labels will be attached to the subject's Blood Collection and Processing Form.
- Using automatical pipets 0.8-1.0 ml of serum put into each of the vials covered with blue caps and 0.4-0.5 ml of serum in vial with green cap.
- Cap all tubes and vials. Put color labels as stated above.
- Record information about the results of processing the samples onto the Blood Collection and Processing Form.

5.2.3.7 INSTRUCTIONS FOR STORAGE AND SHIPMENT OF BLOOD

All processed samples will be stored at -20^{o} C in the refrigerator until they are shipped in the transport cooler to the Central Laboratory. Each storage box will be labeled with a box number and sample type to help identify it in the freezer.

Steps for storage and shipment of the blood samples are as follows:

- Each vial will be stored in a storage box. Vials should be placed into the next available slots within the appropriate storage box, keeping all samples of a particular subject in consecutive slots. The boxes will be filled in serpentine order.
- Once frozen, samples should never be thawed before testing at the Central Laboratory.
- Samples will be stored at -20^{0} C until ready for shipment.
- Information about the storage location of the samples will be recorded onto the Blood Collection and Processing Form.
- Blood samples will be shipped in portable ice chests to the Central Laboratory on a weekly basis.
- A transmittal form will accompany each shipment. The transmittal will list the date and contents of the shipment (listing all ID's and number of vials per ID included in the shipment). A copy of the transmittal will be kept at the local facility and another copy will be sent to the data coordinating center.

5.2.3.8 DATA COLLECTION AND TRANSFER TO DATA CENTER

The blood collection and processing will be documented on the Blood Collection and Processing Form. This form will be pre-labeled with the subject ID and will have a set of specimen ID labels attached. The phlebotomist will label the form with the specimen ID number and will record information about the subject's status with regard to fasting, smoking, exposure to cold and exertion, polyvitamin and medication use, the date and time of the draw, and any problems with the draw. The phlebotomist may also maintain a blood collection log at the phlebotomy station in which the fact of each blood collection will be recorded.

The Blood Collection and Processing Form will accompany the sample to the processing station, where information will be recorded by the laboratory technician regarding processing and storage. The form will then go to the data entry specialist for entry into the study computer system. See Appendix A-5-4 for a copy of the Blood Collection and Processing Form and specifications for its completion.

If NO blood sample is collected, this fact will be recorded on the Control Form and no Blood Collection and Processing Form should be completed.

The blood samples themselves will be shipped to the Central Laboratory accompanied by a transmittal form listing the date of shipment and ID numbers of all samples in the shipment (see Appendix B-5-5). A copy of the transmittal will be sent to the data coordinating center. This will allow the data coordinating center to monitor the shipment of samples and track the receipt of test results. Completed Blood Collection and Processing Forms will also be sent to the Central Laboratory where they will be keyed (for a second time).

5.2.3.9 QUALITY CONTROL FOR BLOOD COLLECTION AND PROCESSING

Quality control for blood collection and processing will be implemented at the local fixed and mobile sites, at the data coordinating center and by the Quality Control Officer:

- Training and certification of the laboratory technicians.
- Ongoing evaluation of the number of unsuccessful draws and failure to obtain adequate samples. If the numbers are high, the reasons and possible solutions will be explored.
- Monitoring fainting or other episodes requiring consultation with a physician, as documented on the Blood Collection and Processing Form or Adverse Events Report.
- Reviewing processing problems reported on the Blood Collection and Processing Form. This will include comparison between the number of required cryovials and those actually frozen, problems with samples that are hemolyzed, icteric, turbid, etc.
- Local monitoring of the temperature of all freezer units. Units will be checked at the beginning and end of each working day, and appropriately logged.
- Monitoring of samples prepared and shipped outside the protocol window.
- Local review of incomplete or incorrect Blood Collection and Processing forms.
- Comparison of data from the Blood Collection and Processing Forms keyed locally with that keyed at the Central Laboratory.
- Reviewing the results from the laboratory testing to assure that collection, field processing, field storage and transport procedures are providing adequate samples for the test procedures, and long-term storage.
- Direct observation of collection, processing, storage and shipment procedures by the Quality Control Officer (or designee). The Quality Control Officer will review training procedures and directly observe collection and processing in the field no less frequently than each 3 months in the first 2 years of the project.

5.2.4 ULTRASOUND EXAMINATION

Ultrasound examinations will be carried out on each subject annually to diagnose thyroid abnormalities. The examinations will be conducted by certified MD ultrasonographers. The ultrasonographer will first, however, perform the thyroid palpation examination (see Section 5.2.5) and document palpation findings on the Palpation Examination Form.

5.2.4.1 RATIONALE

The ultrasonographic examination will be used to characterize the entire thyroid gland and as a diagnostic test for abnormalities of the thyroid in terms of size and shape. It will be used to identify subjects with lesions that should be biopsied and will provide an analytic tool for investigating the pathogenesis of thyroid disease. Thermal print (TP) images of abnormal findings and magneto optical disks (MOD) for all images will provide documentation of findings and be used with quality assurance phantoms for quality control.

5.2.4.2 EQUIPMENT AND SUPPLIES

The equipment and supplies needed for the ultrasound examination are as follows:

- Toshiba Imaging Equipment (Toshiba SSA-240 Ultrasound imaging system with 3.5 MHz linear array deep focus transducer, and 7.5 MHz Linear array -- or equivalent) at each location with 3M image buffer (MOD) and thermal printer device.
- 3M Kitecho Standoff No. 3520
- matrix printer, film and film development system
- sterile acoustic jelly
- QC phantoms
- thermal printer paper
- alcohol swabs
- cloth rolls or bolsters
- Ultrasound Examination Form
- ID labels

5.2.4.3 TRAINING AND CERTIFICATION OF PERSONNEL

Five MD ultrasonographers will receive additional training for lengths of time dependent upon their prior experience and training. In order to conduct examinations for the study, certification will be required. Certification will be carried out by an experienced ultrasonographer based on ten consecutive ultrasound examinations performed on patients with a mix of ultrasonographic abnormalities and normal findings. Annual recertification will also be required.

After certification has been carried out, the names, dates and certification status of all examiners will be documented. This documentation will be kept on file at the data coordinating center. The data coordinating center will track the status of certification and advise individuals and the Director when recertification is required. In addition, once the ultrasound machines are purchased, there will be on-site training in use and care of the equipment by the manufacturer.

5.2.4.4 INSTRUCTIONS FOR ULTRASOUND EXAMINATION

Each thyroid imaging study will be performed with the thyroid 7.5 MHz probe using acoustic jelly as the coupling media.

The subject will be examined supine, with neck extended by cloth roll or bolster. The examination will include evaluation of both lobes of the thyroid gland in transverse and sagittal projections, parathyroid glands (if identified) and superficial and deep cervical lymph nodes.

A series of standard images will be recorded on magneto optical disk (MOD) regardless of whether an abnormality is present or not. The views taken should be done in a standard order as follows:

1. Transverse scan of lower pole (right and left lobe)
2. Transverse scan of isthmus demonstrating as much of both right and left lobes as possible.
3. Transverse scan of upper pole (right and left lobe)
4. Sagittal scan of right lobe through the plane of the greatest cranio-caudal dimension.
5. Sagittal scan of left lobe through the plane of the greatest cranio-caudal dimension.

When abnormalities are noted, additional images will be obtained which delineate the lesion(s).

For subjects requiring evaluation of the parathyroid gland(s) (i.e., suspicion of parathyroid adenoma or history of hypercalcemia) particular attention should be directed posterior to the thyroid gland to detect any mass. Masses should be documented and measured in orthogonal planes. The carotid sheath, which includes the common carotid artery, internal jugular vein and deep cervical lymph nodes, should be imaged to document any enlarged lymph nodes.

The position of the transducer should be registered on all subject's images using the body mark system of the ultrasound device.

A series of standard measurements will be taken to determine thyroid volume as follows: anterior-posterior (a) and transverse (b) dimensions of each lobe on the largest transverse scan; the largest cranio-caudal (c) dimension of each lobe on the sagittal scan. Thyroid lobe volume calculations will be made based on the following formula:

$$V = 0.479 * a * b * c \ (cm^3)$$

Total thyroid volume will be calculated as a sum of the right and left lobes. The isthmus volume should be taken into account if its anterior-posterior dimension is over 5 mm. The measurements of nodule volume will be performed in a manner similar to the lobe volume.

Thyroid volume will also be evaluated by comparison with the referent data taking into account sex and age. The result will be expressed in percent to the defined normal range. Percent will be calculated according to the formula:

V of the subject/normal V, where normal V is an interval V min-V max (100%). For example if the thyroid volume of the subject is increased the percent is calculated as V of the subject/V maximum If the thyroid volume is decreased, it is calculated as V of the subject/V minimum.

Completion of the ultrasound examination will be documented on the Control Form and the subject sent to the next station.

5.2.4.5 DATA COLLECTION AND TRANSFER TO DATA CENTER

Findings of the ultrasound examination will be recorded on the **Ultrasound Examination Form**. This form will be pre-labeled with the subject's ID number. The examiner (or his assistant) will record the instrument settings used for this subject along with the ultrasound findings using the data items and response categories provided on the form. See Appendix A-5-5 for the form and its specifications.

In addition, the data will be permanently recorded on the imaging system's magneto optical disk (MOD) and on temporary thermal prints. The thermal prints, each labeled with a subject ID label, will be attached to the Ultrasound Examination Form. If the patient is referred to the hospital, copies of the images showing the abnormality will be sent along to the hospital.

All files and documents must be labeled for identification purposes. Each MOD will be numbered along with the number of the ultrasound unit on which it is being used. The directory of studies will be established by the operator using software that will be provided with the system.

Within each exam (patient) there is the possibility of recording n images, the number of which can vary from patient to patient. In each image, the patient name, ID and other information (to be defined) will be entered from the keyboard, at the time the exam is conducted (*unless the ultrasound machine is equipped with a barcode reader*).

(NOTE 1: With an EPROM the manufacturer could provide to be inserted into the machine, the directory structure could be changed and simplified.

The Ultrasound Examination form, thermal prints and MOD will initially be reviewed at the local center to determine if any findings require follow-up. The data form will be keyed locally by the data entry specialist. The MOD disks will be transferred to the data coordinating center for archiving, analysis and film preparation for selected cases. The prints taken in the field will stay with the subject's record.

5.2.4.6 QUALITY CONTROL

A number of quality control procedures will be implemented to help ensure that the staff, equipment and examination procedures are performing to high standards.

5.2.4.6.1 QUALITY CONTROL OF EXAMINERS

Quality control procedures for the ultrasound examination staff include the initial training and certification of examiners and annual recertification (see Section 5.2.4.3), direct observation of ultrasonographers, comparison of results obtained by different examiners and comparison of findings of the examiners with results of any referral examinations.

5.2.4.6.2 QUALITY CONTROL FOR EQUIPMENT

The quality control protocol for the equipment is designed to establish that the system is working as expected. This includes the ability of the system to detect standard test objects, to resolve nearby structures, and to establish accuracy of the measurement "calipers." This is particularly important for field systems where boards in the system may be jarred loose in transport, transducers damaged, or other electronic damage incurred.

The following frequency of testing of the system will be carried out:

- **Mobile Stations** - Testing will be done each day that the system is moved. It will be performed at the new site before the first study subject is imaged.
- **Fixed Stations** - Testing will be done monthly and whenever there is a reason for concern.

The thyroid transducer used for thyroid imaging will be evaluated at the nominal operation gain settings with the ATS Model #550 Multipurpose Small Parts Phantom. Direct coupling of the transducer should be done through acoustic jelly. (Note: Since the velocity of sound is temperature dependent, it is important that the ultrasound test phantom be at room temperature for the caliper measurements to be accurate. If left outside (i.e., in a vehicle in the winter especially), it may take as long as 24 hours for the test object to return to standard sound velocity.)

Testing steps are as follows:

1. An image of the vertical-horizontal line targets should be made and recorded on MOD. The horizontal and vertical spacing should be recorded in the near and far field, and compared to previous measurements on

a log kept with the system. The lowest optimal gain settings should be used which get the best images of the targets as higher gain will broaden the appearance of the target size. (*Note: The final manual will include sample images of the kind that should be collected.*)

2. An image of the axial-lateral resolution arrays should be made and inspected to ascertain whether the system performance has changed in a noticeable manner. The same gain settings as noted in step 1 should be used.
3. An image of the cystic target structures should be recorded and viewed, to visually verify acceptable performance and recorded on MOD. These images should be recorded using standard preset imaging factors at each time, as these images are very gain dependent. All machines used on the project should use the same set of factors to permit inter-comparisons of system performance.
4. The same recording factors used in step 3 should be used to acquire and store images of the gray scale target structures.

The other ultrasound probes will be evaluated and dimensional and resolution properties verified on a less frequent, monthly basis, with the imaging procedures noted above.

If the conduct of these quality control measurements takes more than 15 minutes per day to accomplish, the target structure measurements may be performed on a weekly basis, or more frequently, when there is suspicion that device performance has changed. Images of test phantom response should be recorded on thermal prints (as well as MOD) whenever problems are encountered for communication with the service personnel who will need to be contacted to determine the cause of the problem, and to fix it. Depending on field experience with probe integrity, it may be necessary to have a spare linear probe with mobile systems.

The test data recorded on MOD will be returned to the data coordinating center at the end of each trip. A computer analysis of the quality control studies will be performed by the data coordinating center and results which indicate deteriorating performance will be reported to field teams as soon as possible following receipt of the MOD recorded data from the field. Depending of the severity of the problem, this would result in initiation of a request for a service call.

Hard copy prints of the abnormal studies can be generated on a postscript printer in the DCC. Photographs of the monitor screen may be made for slide presentations at meetings and for publication purposes. In subsequent years, a suitable photographic device can be attached to the workstation for this purpose. The acquisition of a video output board, such as the Radius video vision, on the PC used for MOD analyses would permit connecting a thermal printer that would permit generation of additional low cost, relatively high quality records for internal use. Since the original data are stored digitally, the impermanence of the thermal prints is not a serious problem.

Particular attention will need to be devoted to assessing and correcting for changes in caliper readings for gland size and nodule dimensions. Gland size calculations will be made based on maximum dimensions in each lobe sagitally and horizontally based on formula in current use (see Section 5.2.4.4), using the computer adjusted dimensions. In order to establish the relevant correction factors it will be necessary to identify relevant factors on the Ultrasound Examination Form.

5.2.4.6.3 QUALITY CONTROL OF EXAMINATION FINDINGS

Initially, nodule size will be determined visually by a thyroid ultrasound expert viewing the computer data and delineating nodule borders manually. Staff of the data coordinating center will develop automated feature extraction methods using edge detection and texture analysis tools which duplicate the performance of the human expert. The computer based results will be entered into the subject's computer record. Periodic verification of the correspondence between human and computer entries will be made as part of the quality assurance program.

All images in which abnormalities have been noted will be reviewed at the designated referral center on a high quality workstation CRT monitor. Any differences in interpretation will then be noted and entered into the computer-based subject record. A sampling of allegedly normal records will be reviewed in a similar fashion as part of the quality control program of the field work. This will be done on a quarterly basis so that serious problems can be detected and corrected early and continuously throughout the study. The sampling should include all the ultrasound units, and all the different operators.

Hard copies of images of pathological findings in the thyroid will be printed out from the Silicon Graphics system.

Each MOD will have an identifier number assigned as described above, and the directory will identify the subject and his/her location on the disk. MOD disks will be archived for periods of active use, 3-6 months initially, at which time their contents will be transferred to DAT tape and CD-ROM for long-term archiving, and the MOD cartridges recycled to the field.

(Note: The computer systems in the DCC and in the ultrosound clinic area on which the MOD drive is mounted for data analysis needs also to be the one with the DAT tape for ease of image transfer.) Images will be transferred to the Silicon Grafics System for image analyses using CD ROMs prepared in the DCC. The DCC system will be used for Quality Assurance monitoring of the ultrasound devices.

5.2.5 THYROID PALPATION EXAMINATION

Each subject will receive two thyroid palpation examinations. These examination will be performed by two examiners, one of whom will be the ultrasonographer. The examinations will be done to assess thyroid size and structural characteristics of the gland and adjacent neck structures. The ultrasonographer will do the palpation examination **before** doing the ultrasound.

5.2.5.1 RATIONALE

The purpose of the palpation examination is to determine the size of the thyroid gland, the presence and location of structural changes in the thyroid gland and the presence and location of abnormal lymph nodes in the neck. The results will be used in conjunction with those obtained by ultrasound examination.

5.2.5.2 EQUIPMENT AND SUPPLIES

Findings of the thyroid palpation examination will be recorded on the **Thyroid Palpation Examination Form**. No other equipment or supplies are needed for this examination.

5.2.5.3 TRAINING AND CERTIFICATION OF PERSONNEL

The palpation examinations will be carried out by the endocrinologist and the ultrasonographer. A designated trainer-endocrinologist will train and certify all examiners working on the study. During the training period, the trainer will demonstrate the steps in inspection, palpation and recording of results as described below, will observe the trainee carrying out several such examinations and will correct any variations in technique.

For certification, the trainee will independently examine at least ten subjects, some with and some without thyroid abnormalities and will record the results. The trainee will be considered certified when he consistently obtains the same findings as the trainer. Recertifications will be required at intervals of one to two years.

The certifying endocrinologist will document the names, dates and certification status of all examiners tested. This documentation will be kept on file at the data coordinating center. The data coordinating center will track the status of certification and advise individuals and the Director when recertification is required.

5.2.5.4 INSTRUCTIONS FOR THE THYROID PALPATION EXAMINATION

The examinations will be performed independently by the endocrinologist and the ultrasonographer. The ultrasonographer will not share the results of the ultrasound examination, or his palpation with the endocrinologist until the endocrinologist has completed his examination. A combined "final opinion" representing the consensus of the endocrinologist and the ultrasonographer will result from the individual examinations completed by the two examiners (see below Section 5.2.5.4.1).

Steps are as follows:

- Stand or seat the subject in front of the examiner in a good lateral light that accentuates the shadows of the normal structures. The entire neck should be visible down to the sternal notch (collars removed), with the examiner's eyes approximately at the level of the notch.
- Observe whether the gland is visible with the neck in the normal position or only when the neck is extended.
- Inspect the gland for any nodularity. If the gland is enlarged, determine whether it is visible from a distance.
- Palpate the gland initially from the front. First determine whether the trachea is in the midline at the sternal notch.
- Locate the isthmus just below the cricoid cartilage and gently palpate the thyroid lobes at each side of the isthmus using the thumbs or the fingers.
- Turn and flex the neck toward the side being examined while gently pushing on the thyroid cartilage from the opposite side.
- Repeat the palpation while the subject swallows. When necessary for better definition, repeat the palpation with the examiner behind the subject.
- Palpate the entire front of the neck, from the jaws to the clavicles, and the back of the neck for lymph nodes. The examiner may be in front or in back of the subject or in both locations.
- Record the findings of the examination on the Thyroid Examination Form.

5.2.5.4.1 COMPARISON WITH ULTRASOUND

After the palpation results are recorded independently by the two examiners, the results will be disclosed and studied by the endocrinologist. Any discrepancies between the two examiners will be resolved by discussion and re-examination of the subject to reach consensus. Any discrepancies that remain unresolved will be handled as follows:

- A discrepancy between no enlargement of the thyroid and goiter grade IA or between goiter grade IA and grade IB will be registered to the **higher grade**.
- Discrepancies between the two examiners concerning patients with goiter grade IB and grade II or between a palpable nodule and negative findings should be reevaluated at the endocrinology clinic before the next visit.

The consensus achieved will be recorded as the diagnosis on the **Preliminary Summary of Medical Findings and Recommendations**.

When the endocrinologist's examination is completed, an indication will be made on the Control Form and all completed forms remaining for the subject will be held for pick-up by the data entry specialist.

5.2.5.5 DATA COLLECTION AND TRANSFER TO DATA CENTER

Findings of the palpation examination will be recorded on the **Thyroid Palpation Examination Form**. For a standard examination, there will be two such forms completed, one by each of the two examiners. Appendix A-5-6 provides a copy of the form and specifications for its use. The endocrinologist will also complete the Preliminary Summary of Medical Findings and Recommendations which will indicate any diagnosis made and the need for referral in the judgement of the endocrinologist. All forms will be labeled with the subject's ID number and will be keyed locally into the study computer system.

5.2.5.6 QUALITY CONTROL

Quality control procedures for the thyroid palpation examination will be implemented by the quality control officer and will include the following measures:

- Training and certification of examiners.
- Recertification of examiners on an annual or biannual basis.
- Conduct of each exam by two independent examiners.
- Evaluation of sources of variation in the keyed data.
- Direct observation of the examiners.

5.2.5.7 PROVIDING RESULTS TO THE STUDY PARTICIPANT/EXIT PROCESS

After the specimen collection and thyroid examinations are completed, the endocrinologist will discuss initial findings with the subject (and his parents, if present) and provide a written copy of the **Preliminary Summary of Medical Findings and Recommendations** at that time or by mail. This form will be completed using information immediately available from the ultrasound and palpation. The subject will be informed as to whether he needs immediate referral to the hospital, a check-up in 3-6 months, repeat examination in one year or simply that the examiner is waiting for the laboratory results. A copy of the preliminary summary will remain in the subject's chart. The form and its instructions appear in Appendix A-5-7. The physician will answer any questions and clarify any information that the subject or his parents find unclear. The subject will also be told that a **Final Endocrinologic Summary and Recommendations** will be sent to his home and to his home polyclinic as soon as the results of the laboratory tests are available. Following this, the subject will be thanked for his participation and the visit will be concluded.

5.2.5.8 PEDIATRIC/ADULT EXAMINATION

Following the thyroid examination, the subject will receive a general pediatric/adult examination and may be referred to the appropriate polyclinic or dispensary in the event of positive findings requiring further study. The pediatric/adult examination is not part of the research protocol.

5.3 REPORTING RESULTS TO HOME POLYCLINIC

After laboratory test results are available, a copy of the **Final Endocrinologic Summary and Recommendations** will be mailed to the subject's home polyclinic. See Chapter 7 for more information.

5.4 REFERRAL FOR FINE NEEDLE BIOPSY

Subjects with thyroid nodules or focal lesions of a specified size revealed by palpation or ultrasound examinations will be referred for fine needle biopsy.

5.4.1 CRITERIA FOR REFERRAL

All thyroid nodules or focal lesions revealed by palpation or ultrasonography that are **1 cm or larger** at their greatest diameter will be referred for biopsy. In children under age 12, fine needle aspiration will be done on nodules **larger that 5 mm**. If diffusely altered echogenicity is present on ultrasonography, accompanied by one or more abnormal pretracheal, paratracheal, or parajugular lymph nodes not explainable by intercurrent disease, fine needle aspiration of the thyroid and one or more accessible nodes will be done.

5.4.2 EQUIPMENT AND SUPPLIES

The following equipment and supplies are required for the fine needle biopsy or aspiration:

- Disposable syringe, one per puncture
- Pair of disposable gloves, one per puncture
- Disposable needle (25G), one per puncture
- Disinfective noniodine-containing spray suitable for ultrasound examination
- Microscope slides, 3-5 per puncture
- Spray-cyte

- Slide holders
- Staining solution and equipment
- Needle Biopsy Form

5.4.3 TRAINING AND CERTIFICATION OF PERSONNEL

Fine needle biopsy will be done by an ultrasonographer under ultrasound guidance. For training purposes, the trainee will perform fine needle biopsy under the supervision of an expert on 12 patients. The trainee will be required to demonstrate the ability to obtain satisfactory specimens in >50% of cases.

5.4.4 NEEDLE BIOPSY PROCEDURES

Fine needle biopsy will be performed only in a designated center, and may be done under ultrasound guidance. If identical multiple nodules are identified manually, all nodules will be biopsied..

Subjects may be prepared for the procedure by use of an oral tranquillizer. They will have the option of refusing the tranquillizer. The subject will be instructed to refrain from swallowing or talking during the procedure.

The subject will be in the supine position with a pillow placed under the shoulders in order to extend the neck and increase exposure of the gland. Local anaesthesia is not required. The skin will be prepared with a noniodine-containing antiseptic solution suitable for ultrasound examination.

The skin will be penetrated with a fine 25 gauge needle attached to a 10 ml syringe. A special device attached to the transducer of the ultrasound machine may be used. Sampling should be performed with short back and forth movements of the needle through the lesion. If the material does not appear in the needle hub, suction will be applied. The syringe plunger should be released, relieving the vacuum, before withdrawing the needle. Gentle pressure will be applied to the aspiration site to reduce the chance of hematoma formation.

The aspirated material will be transferred to glass slides pre-labeled with the subject's ID number. To prepare the slides, one or two drops of the aspirated material should be expressed onto a clean slide using the 1 cc of air previously drawn into the syringe. Then a second slide should be placed on top of the first slide and after the material spreads, the two slides should be pulled apart in a horizontal plane.

The slides should be air-dried or fixed by spray-cyte until staining with Giemsa. As each slide is prepared, it will be marked with a letter (A, B, C, etc) to indicate the site from which it was aspirated and the letter and corresponding site will be recorded on the **Needle Biopsy Form**.

Adequacy of the specimens will be immediately verified by the cytologist or endocrinologist himself. The smears should be considered to be adequate if a minimum of two slides demonstrate six to eight cell clusters. If the specimen is determined to be inadequate, another attempt will be undertaken. The maximum number of attempts per session is two per nodule. If the second attempt fails, depending on the endocrinologist's findings, the subject will be recalled in 3 to 6 months, or perhaps even referred for surgery if there are signs of metastases. At the next examination, fine needle biopsy will be repeated in subjects with persistent nodules in whom cytological findings were benign or indeterminate. In the presence of clinical features indicating disease progression, further management will depend on the clinical judgement of the endocrinologist.

The stained slides will be interpreted by the cytologist.

5.4.5 POSSIBLE ADVERSE EVENTS FROM FINE NEEDLE BIOPSY

Possible adverse events resulting from the fine needle biopsy might include:

- pain
- fainting
- hysteria
- transient damage to the laryngeal nerve
- puncture of the trachea
- laryngospasm
- bleeding

If the trachea is entered during the procedure, the subject may cough and even produce blood-tinged mucus. In this situation, the procedure must be stopped and the subject should be observed by his physician. If the jugular vein or carotid artery is accidentally punctured, pressure should be applied to the site for several minutes to ensure that bleeding has stopped. In all cases, subjects will be handled according to standard medical practice. Every adverse event must be documented on the Fine Needle Biopsy Form.

5.4.6 DATA COLLECTION AND TRANSFER TO DATA CENTER

Findings from the fine needle biopsy will be recorded on the **Needle Biopsy Form**. The form will be labeled with the subject's ID number. The form and its specifications appear in Appendix A-5-8.
Completed Needle Biopsy Forms will be sent to the data coordinating center to be keyed there. Copies of these forms will be kept in the hospitals/clinics where the procedure was performed.

5.4.7 QUALITY CONTROL

Quality control procedures for the fine needle biopsy include:

- Training and certification of physicians who perform the fine needle biopsy
- Review of subjects selected for procedure
- Direct observation of technique
- Quarterly review of all slides by at least one expert cytopathologist for adequacy and accuracy of diagnosis

5.5 DIAGNOSTIC OR THERAPEUTIC REFERRALS FOR OTHER THAN FINE NEEDLE BIOPSY

5.5.1 THYROID REFERRALS TO THE DESIGNATED ENDOCRINOLOGICAL DEPARTMENT

Subjects whose examinations reveal any of the following thyroid abnormalities will be referred to the designated Endocrinology Department.

CLINICAL PRESENTATION/HISTORY:

- all palpable thyroid nodules
- unexplained cervical lymph node enlargement (suspicious for tumor)
- clinical signs of functional abnormalities of the thyroid and/or parathyroid glands
- prior thyroid surgery patients with malignant disease should be referred to the hospital twice a year or any time new metastases are suspected
- prior thyroid surgery patients with benign diseases should be referred to the hospital annually or any time recurrence is suspected

SONOGRAPHIC FINDINGS:

- all nodules and focal lesions in thyroid gland on first detection
- nodules smaller than 5 mm perceived to increase in size under L-thyroxine treatment
- thyroid development abnormalities on first detection

LABORATORY FINDINGS:

- thyroid function tests TSH, which clearly support the diagnosis of hypothyroidism or hyperthyroidism by having two or all of the function tests outside the reference range and in the same "diagnostic" direction, or anti-thyroid antibodies with significantly elevated titres

In case of absolute refusal to be referred to the designated Endocrinology Department, subjects may be referred to specialists at the dispensaries or the local polyclinics.

5.5.2 THYROID REFERRALS FOR REPEAT EXAMINATION

Subjects with any of the following findings will be requested to undergo a repeat examination in six months:

- thyroid nodules smaller than 5 mm in largest diameter after hospitalization
- diffuse moderate decrease of echogenicity
- a laboratory test of thyroid function which has a value outside the reference range after repeat testing or an antithyroid antibody test with a positive but low titre

5.5.3 OTHER ENDOCRINOLOGIC REFERRALS

Other than for thyroid and parathyroid findings, endocrinologic referrals may be made (e.g., diabetes). Subjects may be referred to specialists at the local level. This will be left to the judgment of the endocrinologist performing the exam. Information regarding the condition and referral will be noted in the subject's regular medical record.

5.6 MEDICAL EMERGENCIES, ADVERSE EVENTS

Subjects will be provided with immediate care for any medical emergency which may occur during their visits, whether or not it is related to study procedures.

Adverse events are defined as medical problems occurring as a direct consequence of a study procedure. The study examinations involve minimal risk. Adverse events will be handled according to standard medical practice. In addition, every adverse event not recorded on the appropriate specimen or examination form must be documented on an **Adverse Event Report** (Appendix A-5-9). This report will be sent to the chief endocrinologist, and will eventually be transferred to the data coordinating center. Review of these reports and adverse events reported on other data forms will be important in monitoring the integrity of the study.

6. LABORATORY DETERMINATIONS

This chapter gives an overview of laboratory testing of urine and blood samples collected for the study and describes associated data flow. Detailed laboratory procedures, including equipment specifications and maintenance, assay protocols and quality control procedures are presented in a separate manual (see Master Laboratory Manual).

6.1 IODINE TESTING OF URINE

Iodine testing of urine will be performed for the subject when first screened.

Iodine testing requires an **isolated** laboratory, maintained iodine free with a fume hood and filtered ventilation. Detailed information on the testing protocol can be found in the Master Laboratory Manual.

6.1.1 DATA COLLECTION AND TRANSFER TO DATA CENTER

The urine assay data will be recorded on the Laboratory Results Form (or log) by sample ID number (see Appendix A-6-1). The data will be keyed at the Central Laboratory and the keyed data will be sent periodically to the data coordinating center to allow tracking of the test results and for quality control purposes.

6.2 THYROID FUNCTION TESTS

Thyroid function tests include TSH. Determination of TSH level will be used as a screening test for diagnosis of early hypothyroidism, occult hyperthyroidism and also in the followup of patients receiving suppression and replacement therapy by levothyroxine.

Details on the testing protocol are provided in the Master Laboratory Manual.

6.2.1 DATA COLLECTION AND TRANSFER TO DATA CENTER

The assay results for thyroid function tests will be visually scanned to determine that they fall within an acceptable range, using the procedures outlined in the Master Laboratory Manual. The chief of the Central Laboratory must sign all worksheets to indicate that the results have been reviewed. After this, the results will be reported, by sample ID, on the Laboratory Results Form (see Appendix A-6-1). The results will then be keyed and sent back to the examining center and to the data coordinating center. A hard copy will also be sent to the examining center. Results sent to the examining center will be reviewed by the endocrinologist and used for completion of the Final Endocrinological Summary and Recommendations. Results sent to the data coordinating center will allow the data coordinating center to track test results and perform appropriate quality control functions.

6.3 OTHER BLOOD TESTS

Anti-thyroid antibody tests include anti-TPO.

Details of the testing protocols are provided in the Master Laboratory Manual.

6.3.1 DATA COLLECTION AND TRANSFER TO DATA CENTER

The assay results will be reviewed to determine that they fall within an acceptable range, using the procedures outlined in the Master Laboratory Manual. The chief of the Central Laboratory must sign all worksheets to indicate that the results have been reviewed. After this, the results will be reported, by sample ID, on the Laboratory Results Form (see Appendix A-6-1).

The results will then be keyed and sent to the examining center and to the data coordinating center. A hard copy will also be sent to the examining center. Results sent to the examining center will be reviewed by the endocrinologist and used for completion of the Final Endocrinological Summary and Recommendations. Results sent to the data coordinating center will allow the data coordinating center to track test results and perform quality control functions.

6.4 LABORATORY SUMMARY FOR THE ENDOCRINOLOGIST

Having completed his physical examination and his **Preliminary Endocrinologic Summary and Recommendations** at the time of the participant's visit, the endocrinologist will review the laboratory results in order to complete the **Final Endocrinologic Summary and Recommendations** (see Appendix A-7-1).

Laboratory results will be received via computer file and hard copy from the Central Laboratory. After the results are used to complete the Final Endocrinology Summary and Recommendations form, a copy will be sent to the local polyclinic of the subject and another copy will be filed in the medical record maintained by the study for that participant.

6.5 LONG-TERM STORAGE OF SPECIMENS

All blood specimens will be stored for three months at -20^{o} C. Abnormal bloods or those of subjects with endocrinologic findings will be stored for one year (or longer) at -55^{o} C or lower.

7. FINAL ENDOCRINOLOGIC SUMMARY AND RECOMMENDATIONS

With the completion of the endocrinologic examination, and the final laboratory results in hand, the endocrinologist will prepare the **Final Endocrinologic Summary and Recommendations**. Note that this form is prepared before any biopsy, surgical, or pathology results are available. The Final Endocrinologic Summary and Recommendations will include any preliminary diagnoses and the endocrinologist's recommendations for follow-up and/or treatment. The Final Endocrinologic Summary and Recommendations and specifications for completiong of this form are shown in Appendix A-5-10.

8. ENDPOINT DETERMINATION AND COHORT FOLLOW-UP

8.1 DIAGNOSIS OF THYROID AND PARATHYROID PATHOLOGY

The nodular and diffuse thyroid lesions revealed after clinical examination and laboratory tests will be additionally analysed in order to diagnose thyroid cancer and other thyroid diseases. The diagnosis of benign and malignant thyroid disease at the preoperative period will be established at the Clinical Endocrinological Department, and after surgical treatment it will be verified on histological specimenses at the Pathology Laboratory of the Institute of Endocrinology.

8.1.1 HISTOLOGICAL EXAMINATION

8.1.1.1 INTRAOPERATIVE HISTOLOGICAL EXAMINATION OF BIOPSY MATERIAL USING FROZEN SECTIONS

In the presence of nodular lesions or focal infiltrations of thyroid gland, enlarged cervical lymph nodes, the lesioned thyroid lobe (or its part), the enlarged lymph nodes revealed may be, immediately after surgical ablation, sent to the Laboratory of Morphology for express-diagnostic histological examination. Such an examination is of paramount importance in case of unclear cytologic conclusions with smears obtained as a result of fine-needle aspiration biopsy.

After measuring length, width and thickness of the preparation, the lobe removed or its part must be consecutively cut into slices 4 - 5 mm thick, the maximum diameter of nodules or focal dense areas has to be measured and presence of capsule, capsular invasion, cystic or hemorrhagic foci, etc., is noted.

The lymph nodes removed should be also measured and cut into slices with indication of presence of infiltrated areas, hemorrhages, cysts, etc.

One of thyroid tissue fragments obtained with nodule or focal dense areas as well as one of the fragments of a removed lymph node are placed on specimen discs covered with tissue freezing medium, are frozen with Cryospray and put into the Cryostat. The frozen sections obtained by cryomicrotomy 12 to 15 mcm thick are carried to microscope slides marked with ID number of patient with an additional mark of specimen location (figures 1,2,3, etc.), are quickly fixed in 96 % ethanol, stained using a fast technique with hematoxylin and eosin, and then they are examined by a pathologist at light microscope.

All the procedure from the moment of biopsies' delivery to the Pathology Laboratory till the communication of the results (by phone) to the Surgery Department of the Institute of Endocrinology takes on the average 15 to 30 minutes depending on the number of biopsies sent for express-analysis and the necessary quantity of sections for making a provisional diagnosis.

In order to carry out intraoperative histological express-analysis the following equipment, supplies and reagents are necessary:

- cryostat (freezing microtome);
- microscope;
- disposable gloves;
- tweezers of different size;
- a table for biopsies' preparation;
- disposable blades for biopsies' preparation;
- specimen discs of different surface;
- tissue freezing medium;
- Cryospray;
- disposable blades for Cryostat;
- holders for microscope slides;
- histological glass dishes;
- ethanol;
- xylene;
- hematoxylin solution;
- eosin solution;
- microscope slides;
- coverslips;
- frozen tissue embedding media;

- Pathology Form for histological express-analysis:

8.1.1.2 POSTOPERATIVE HISTOLOGICAL EXAMINATION OF BIOPSY MATERIAL

After completing surgery, all removed material is sent to the Pathology Laboratory. After describing the macrospecimens, the specimens delivered will be cut into slices (see 8.1.1.1) fulfilling the measure-ments given in the Pathology Form: dimensions of lobe, thyroid nodules, infiltrations, cysts, lymph nodes (if available).

The following number of specimens is to be selected for further histological processing:

- in case of diffuse thyroid lesion: 2 to 3 fragments from different lobe areas;
- in case of solitary nodule: all the fragments obtained of nodule tissue (for a nodule up to 2 cm diameter) or 5 to 6 fragments from different nodule areas (for a nodule more than 2 cm diameter), as well as 2 to 3 fragments of extranodular thyroid tissue;
- in case of multinodular lesion: 2 to 3 fragments of each nodule and 2 to 3 fragments of extranodular tissue;
- all the lymph nodes removed.

The specimens obtained are put in plastic cassettes marked with ID number of patient with aditional mark of specimen locations (figures 1, 2, 3, etc.), they are fixed in 10 % neutral formalin, dehydrated in ethanol of increasing concentrations, cleared up in three xylene portions, impregnated with in three paraffin portions (one of them is supplied with a vacuum attachment, and embedded into paraffin. All the procedure of histological processing of specimens is carried out under standard conditions in corresponding tissue processors and embedding centers.

From each of the paraffin blocks obtained, sections 4 to 5 mcm thick (2 to 4 sections depending on the features of the specimen delivered) are obtained on a microtome. these sections are carried to a special water bath, and then to microscope slides. After drying, the preparations are deparaffined in two xylene portions and stained with hematoxylin and eosin using a standard technique in the staining machine. After embedding in Eukit histological mountant, the specimens will be analysed by a pathologist at light microscope (in complicated cases or when verifying diagnosis of thyroid carcinoma, the preparations will be studied by two pathologists).

In order to carry out postoperative histological examination, the following basic equipment, supplies and reagents are necessary:

- tissue processor;
- vacuum unit;
- embedding center;
- microtome;
- water bath;
- staining machine;
- microscope;
- disposable gloves;
- tweezers of different size;
- table for biopsies' preparation;
- disposable blades for biopsies' preparation;
- dishes for preliminary fixation of biopsy material;
- 10 % neutral formalin;
- ethanol;
- xylene;
- hematoxylin solution;
- eosin solution;
- paraffin;
- disposable blades for microtome;
- holders for microscope slides;
- histological glass dishes;
- microscope slides;
- coverslips;
- Eukit histological mountant;
- Pathology Form for postoperative biopsy material analysis;
- computer with line supply.

As far as possible (availability of reagents), biopsy material will be also fixed and processed in order to carry out further electron microscopic examination.

8.1.1.3 DATA COLLECTION AND TRANSFERRING TO DATA COORDINATION CENTER

The results of histological examination have to be entered in a Pathology Form which will be marked with ID number of patient. This Form is given in Appendix A..... The Forms filled in will be sent to the Data

Coordination Center (and tranmitted through computer modem communication). Duplicates of these Forms will be also stored at the Pathology Laboratory(on paper and floppy disks).

8.1.1.4 QUALITY CONTROL

- training of laboratory assistants-histologists performing histological processing of biopsy material, microtomy and staining of preparations;
- training of pathologists involved in verification of diagnoses;
- realization of additional methods of investigation in complicated cases of differential diagnosis: immunohistochemical study with antibodies against thyroglobulin and calcitonin when suspecting a medullary or anaplastic carcinoma; immunohistochemical study with antibodies against Common LA when suspecting a thyroid lymphoma; histochemical study for elastic fibers or immunohistochemical study with antibodies against endothelial cells in order to evidence vascular invasion in case of follicular carcinoma;
- realization of additional examination of histological preparations by leading experts-pathologists;
- creation of special archives of paraffin blocks and histological specimenses (minimum quantity: one block and one histological specimenses from each nodule or tumoral focus, area of extranodular or extratumoral thyroid tissue, metastatically lesioned lymph node). The experts-pathologists will be provided with archives preparations, if necessary, paraffin blocks may be used for carrying out extended morphological studies, for example, using immunohistochemistry and in situ hybridization methods.

8.1.2 DIAGNOSTIC CRITERIA

THYROID CANCER:

The diagnosis of thyroid cancer should be based on the final histology conclusion after thyroid surgery.

As described in Section 5.4, fine needle biopsy will be performed on all palpable nodules and/or focal lesions identified on ultrasound that are 1 cm or larger in greatest diameter in subjects age 12 or older and larger than 5 mm in subjects under age 12 and in patients with diffusely altered echogenicity accompanied by deep cervical lymph node enlargement. If the cytologic diagnosis is "malignant" or "suspicious," surgical excision and histology examination will be undertaken.

An elevated serum level of thyroglobulin is considered suspicious for metastatic thyroid cancer. Subjects with this laboratory result will undergo additional diagnostic procedures to rule out lung and bone metastases. The thyroid gland will also be reexamined by an expert sonographer. Even with only a slight suspicion of malignancy, surgery and histological examination will be performed, or alternatively, the subject will be put on a suppressive dose of levothyroxine and followed at 3 to 6 month intervals.

NODULAR GOITER:

The diagnosis of nodular goiter should be based on clinical findings of any size thyroid nodule confirmed by ultrasound examination and proved to be benign by fine needle biopsy in nodules of the size indicated above. After fine needle biopsy, the diagnosis should be defined by cytologic findings as neoplastic, e.g. possible adenoma or carcinoma, or non-neoplastic, e.g. colloid nodule or cyst.

Subjects with a benign diagnosis on fine needle biopsy or with focal lesions smaller than indicated above, may be placed on thyroid hormone therapy (approximately 2.5 mg/kg levothyroxine per kg of body weight) and followed for 6 months. If the lesion increases in size, the fine needle biopsy will be repeated and the necessity for surgical treatment will be evaluated by the endocrinologist and the surgeon.

HYPOTHYROIDISM:

An elevated TSH combined with lowered T4 or FT4 is diagnostic of hypothyroidism and treatment will be instituted. Mild elevations of TSH only suggests subclinical hypothyroidism. These subjects will be followed closely, with repeat examinations every 6 months.

AUTOIMMUNE THYROIDITIS:

An elevated level of ATPO and/or ATG is suggestive of autoimmune thyroiditis. For a final diagnosis, the ultrasound findings i.e., hypo-, hyperplasia, low echogenicity, will be taken into consideration as well as tests of thyroid function. Serum obtained during the screening examination will be used to measure ATPO. Serum positive for ATPO will be stored for reevaluation and determination of ATG.

HYPERPARATHYROIDISM:

An elevated PTH level indicates hyperparathyroidism. Serum will be used to measure calcium and albumin. Serum of subjects with hypercalcemia will be stored for immunoassay of PTH.

ENDEMIC GOITER:

Clinical or ultrasound findings of enlarged thyroid gland in an euthyroid or hypothyroid subject with normal or subnormal levels of ATPO living in an iodine-defficient area indicates endemic goiter.

Treatment-induced pathology must be diagnosed and includes:

HYPOPARATHYROIDISM:

A decreased level of calcium or clinical features of hypocalcemia in post-operative patients indicates hypoparathyroidism.

LARYNGEAL NERVE DAMAGE:

This diagnosis will be based on clinical findings (e.g. hoarseness, stridor) and laryngoscopy.

8.2 SUBJECT HOSPITALIZATION OTHER THAN STUDY REFERRAL

Hospitalizations will be tracked primarily to identify those related to thyroid and parathyroid disease, both prospectively and retrospectively. For subjects undergoing additional diagnostic evaluation and treatment as a result of study examination, study staff will have knowledge of the details of the hospitalization (see above). All other subjects will be questioned during the interview part of the examination visit about any hospitalizations in the past. In the baseline year, this will include all prior hospitalizations. At each annual visit, it will include hospitalizations in the past year. If the hospitalization was related to a thyroid problem or there is any suspicion that the hospitalization was related to a thyroid problem, the medical records from that hospitalization must be obtained for review. The data coordinating center may be involved in the procurement of these medical records. Tests performed, surgical procedures and diagnoses will be abstracted onto the **Hospitalization Abstract Form** by the endocrinologist assigned to the subject when such records are available. Records available only elsewhere will be abstracted by personnel of the epidemiology group and reviewed by the study endocrinologist. The Hospitalization Abstract Form and instructions for its completion are shown in Appendix A-8-1

Once completed, the form will be sent to the data coordinating center for processing. A copy will also be sent to the subject's home polyclinic.

8.3 DEATH

All deaths occurring among members of the study cohort will be identified and the cause of death will be determined by review of the death and medical records. The aforementioned review of death and medical records will be carried out by the personnel of the epidemiology group. The data will be keyed at the data coordinating center and the abstracts filed in the subjects charts.

8.3.1 NOTIFICATION OF STUDY OF SUBJECT DEATH

Deaths will be ascertained in a number of ways.

These include:

- Notification by the family. This may happen in response to the letter sent to the subject to schedule an appointment.
- Follow-up of thyroid cancers diagnosed as part of the study procedures.
- Notification from the local polyclinic. Each polyclinic will be provided with a list of subjects in its jurisdiction and asked to notify the study in the event of death. These lists will be updated annually to reflect address changes.
- Periodic linkage with the Chernobyl Registry.
- Review of computerized file of deaths. Assuming such a file becomes available for Ukraine, this file will be linked to the study cohort file periodically to ascertain deaths.

8.3.2 OBTAINING PERTINENT RECORDS

For each study subject who dies during the course of the study, information regarding the cause of death will be obtained. First, the death certificate will be obtained. If the subject died of disease, a copy of any terminal hospital record will be obtained for review. If an autopsy has been performed, and thyroid tissue retained, it will be important to obtain a block of thyroid tissue. Thyroid tissue will be sought regardless of cause of death.

If death is in any way related to thyroid disease, to any treatment for thyroid disease, or to metastasis from a primary thyroid cancer, full clinical details will be sought from any hospitals where the subject was treated, and will be documented on the **Death Data Form** (see Appendix A-8-3 for the form and its specifications).

8.3.3 EXPERT REVIEW OF DEATH DATA

At periodic intervals, files on deaths occurring in that interval will be reviewed by an expert group appointed by the director and representing relevant medical specialities including endocrinology, surgery, pathology and internal medicine.

9. DATA MANAGEMENT

This chapter describes data management activities for the study. It includes an overview of the role of each participating organization in data management, presents software and forms to be utilized and discusses data processing and reporting functions. Detailed specifications for data management and data processing systems are provided in a separate manual entitled, Data Management Manual.

9.1 OVERVIEW OF DATA FLOW

Data for the study will be collected on paper forms with codes designed for ease of computer entry and many of which will then be keyed into the computer at the location where the examination is performed. Computer entry should be accomplished whenever possible while the subject is still in the area so that ambiguous entries may be clarified before computer entry. Following quality control checks, the paper records of the visit will usually be filed at the place where examinations are performed, and to which the mobile units are attached. Laboratory test results will generally be keyed and filed at the Central Laboratory.

Once the data have been entered into the computer and adequately verified (see Section 9.3), they will be transmitted to the Data Coordinating Center by means of weekly mailings of diskettes. Later in the life of the study, data transfer from places of examination may be accomplished by telephone lines and modems.

Paper files will be kept in locked files or locked areas and in study-number sequence. Computer files will be accessed only by passwords issued to those with a "need to know" by the authority of the Project Director.

9.1.1 STAFF RESPONSIBILITIES FOR DATA MANAGEMENT

Outlined below are the data management responsibilities of the Data Coordinating Center, the fixed examination centers, the mobile units, the Central Laboratory and the Epidemiology Group.

RESPONSIBILITIES OF THE DATA COORDINATING CENTER

- Establishment of the cohort
- Training the staff to work with PC
- accession the selection made by the dosimetry group
- update individual records with identifying information from other sources
- update file with tracing efforts and their results
- Allocation of subsamples of the cohort to examining groups on geographical basis
- Design systems for specimen identification and for identification of data collection and other forms
- Make appointments with study subjects
- Print and mail contact and appointment letters
- reschedule appointments as necessary
- prepare registration logs for examining teams
- Design and prepare forms, labels, and other study materials
- design bar-code system
- prepare and distribute data collection and management forms
- design, print and distribute subject ID and specimen labels
- entry of forms not keyed by examining units
- repeat entry of forms keyed at examining units for quality control checks

QUALITY CONTROL OF THE FOLLOWING ACTIVITIES:

- editing, coding and data entry
- shipment of specimens and data collection forms
- inventory subsystem
- ultrasound images
- referral of specimens to outside laboratories

CONTROL OF STAFF CERTIFICATION

TRACK DELIVERY AND DISTRIBUTION OF EQUIPMENT

REPORT ON THE PROGRESS OF THE STUDY:

- provide and maintain an automated study management system for use by the examination centers
- prepare and distribute reports from the study management system
- track laboratory specimens

COMPILE AND MAINTAIN THE STUDY DATABASE:

- provide and maintain coding, keying, editing and data backup specifications and programs to the examination centers
- handle incoming data from the examination centers
- review coding/keying/editing decisions made by the examination centers and ensure consistency across the centers
- act as the prime contact for data-related issues and technical questions
- provide support for statistical and clinical requests

RESPONSIBILITIES OF THE EXAMINATION CENTERS

HANDLE LAST-MINUTE CHANGES IN APPOINTMENTS WITH STUDY SUBJECTS

MANAGE THE PAPER FLOW FROM STUDY VISITS:

- prepare/update locator forms with subject contact information
- code and key completed data forms
- edit keyed data using programs developed by the Data Coordinating Center
- send the coding/keying decision log to the Data Coordinating Center on a monthly basis for review
- organize weekly mailings of study data to the Data Coordinating Center
- file medical records generated by the study

TRACK SPECIMEN COLLECTION, PROCESSING AND SHIPMENT:

- key completed specimen forms and ship forms and specimens to the Central Laboratory
- enter specimen tracking information into the database
- run specimen check programs and resolve discrepancies
- generate transmittals to accompany the shipment of specimens and send the transmittals, along with the samples, to the Central Laboratory

TRACK SUBJECT PARTICIPATION STATUS:

- maintain registration logs
- complete and update, as necessary the Locator Form, Missing Data Form and Non-response Form
- enter participation status information into the study management system

RESPONSIBILITIES OF THE MOBILE UNITS

MANAGE THE PAPER FLOW FROM STUDY VISITS:

- code and key completed data forms
- prepare/update locator forms with subject contact information
- edit keyed data using programs developed by the data coordinating center
- return study data to the fixed examination center to which the mobile unit is attached for filing and transmittal to the data coordinating center

TRACK SPECIMEN COLLECTION, PROCESSING AND SHIPMENT:

- key completed specimen forms
- enter specimen tracking information into the database
- run specimen check programs and resolve discrepancies
- return specimen forms and samples to the fixed examination center to which the mobile unit is attached for shipment to the Central Laboratory

TRACK SUBJECT PARTICIPATION STATUS:

- maintain registration logs
- complete and update, as necessary the Locator Form, Missing Data Form and Non-response Form
- enter participation status information into the study management system

RESPONSIBILITIES OF THE CENTRAL LABORATORY

RECEIVE BLOOD AND URINE SAMPLES, FORMS AND TRANSMITTAL LOGS

ENTER SPECIMEN TRACKING INFORMATION INTO DATABASE

RECORD TEST RESULTS ON LABORATORY RESULTS FORMS AND KEY INTO STUDY COMPUTER SYSTEM

INVENTORY CONTROL OF LABORATORY SUPPLIES AND EQUIPMENT

RESPONSIBILITIES OF THE EPIDEMIOLOGY GROUP

ESTABLISHMENT OF THE COHORT:

- cooperate with the data coordinating center in obtaining identifying information
- plan and carry out tracing efforts to locate subjects
- collecting information on death events.
- to coordinate work with local medical clinics.
- to coordinate work with non-response cases
- define parameters for Cohort Selection
- collect information on hospitalisation

FOLLOW-UP WORK

- on non response
- on migrants

OTHER FUNCTIONS

- reporting
- analysis

9.1.2 QUALITY CONTROL FOR DATA MANAGEMENT

Quality control will be exercised by the data coordinating center and the Central Laboratory on the basis of statistical analyses of the individual operations and of their inter-relationships. In addition, certain operations may be repeated, and double-keying will be practiced, at least initially in order to establish error rates. Further details of the data management quality control plan are provided in subsequent sections of this chapter.

9.2 FORMS AND SOFTWARE

9.2.1 FORMS

There are two types of forms used for the study: management forms and data collection forms. Management forms are used to document and support administrative aspects of the study. Data collection forms are used to record information collected from and about individual study participants. The specific forms, their use and disposition are described below. A form manual will be prepared and maintained.

Management forms: These are forms which provide information for the management of study activities.

- A **consent/assent form** will be used to document that the subject has agreed to participate in the study. It will be signed by the nurse or interviewer who administers it. It will be filed in the subject's study file at the local center. Appendix B-5-1.
- The **Locator Form** will be used to record identifying and tracking information about the subject. Information on this form will assist the Epidemiology group in finding the subject in subsequent years of the study. It will be keyed into the study management system at the data coordinating center and updates will be sent to the data coordinating center by the examining centers as they are obtained. Appendix B-5-2.
- The **registration log** will be maintained at the registration desk to record the flow of subjects for examination, missed appointments, arrivals prior to appointment, etc. This log will be generated by the data coordinating center as it is responsible for appointment scheduling. After completion, it will be returned to the data coordinating center so that action can be taken on missed appointments and other non-response situations. Appendix B-5-3.
- The **control form** carried by the subject from station to station and on which the fact of examination at each station is recorded. It will contain the reason why any examination was not performed. This form is

left at the final station when the subject has completed all examinations. It will be keyed and filed at the local examination center and the data sent to the data coordinating center. Appendix B-5-4.

- **Transmittal forms** will accompany shipments of urine and blood samples to the testing laboratories. These forms will indicate the date and contents of the shipment. Information from the transmittal will be entered into the study management system at the local examination center and at the Central Laboratory and sent to the data coordinating center so that samples can be tracked. Appendix B-5-5.
- A **nonresponse form** will be completed by the data coordinating center, medical support facility or epidemiology group to document information about a subject who will not be participating in a particular year or a subject who is lost to follow-up, or told that he/she refuses to participate at all, or if he/she didn't show up in appointment time. This form will be keyed into the study management system at the data coordinating center. Appendix B-9-1.

Data collection forms: These are the forms on which the study data will be entered. They include:

- The **initial abstract form** on which is recorded basic demographic, relevant medical and identifying information about the study subject collected as the cohort is assembled. Information on this form will be keyed and compiled by the data coordinating center. Appendix A-3-1.
- The **initial interview form** on which is recorded prior medical history and exposure information useful for dosimetry. This form will be keyed at the local examination center (*or epidemiology group or data coordinating center? - and filed where?*). Appendix A-5-1.
- The **annual interview form** on which is recorded information about health events occurring in the past year. This form will be keyed locally and filled their. Appendix A-5-2.
- The **urine collection and processing form** to record the fact of the collection, any reason for inadequacy or absence of the sample, and the subsequent processing and shipment of samples to the Central Laboratory. This form will be filed at the local examination center and transferred to the DCC. Appendix A-5-3.
- The **blood collection and processing form** to record the fact of the collection, any problems, and the subsequent processing, storage and shipment to the Central Laboratory. This form also moves with the collected specimen to the Central Laboratory. It will be keyed and filed at the local examination center and transferred to the DCC. Appendix A-5-4.
- The **ultrasound examination form** on which will be recorded the findings of this examination. In addition, images will be recorded into computer files and transferred to the study computer. The form will be keyed and filed at the local examination center. Appendix A-5-5.
- The **thyroid palpation form** will be used to record the results of the ultrasonographer's and endocrinologist's examination of the thyroid and the surrounding area. This form will be keyed and filed at the local examination center. Appendix A-5-6.
- The **Preliminary Summary of Medical Findings and Recommendations** which will be given to the subject at the end of the visit to summarize the medical findings and provide any necessary recommendations. This form will be keyed at the local examination center. A copy of this summary will be filed in the subject's chart. Appendix A-5-7.
- The **adverse event report** will document adverse medical events, not reported on an examination data form, which result from a study examination/procedure and/or occur during a visit to the examination center. Appendix A-5-9.
- The **laboratory results forms** on which the Central Laboratory will enter the results of the various tests prescribed by the research protocol for both urine and blood. These may be paper forms or computer files. If paper, they will be keyed at the Central Laboratory. Data files will then be sent to the appropriate local examination center and the data coordinating center. Appendix A-6-1.
- The **Final Endocrinologic Summary and Recommendations** which is completed by the endocrinologist after the laboratory results are received and summarizes the final findings and recommendations of the examination and testing. It will be keyed at the local examination center. Copies will go to the subject, the subject's home polyclinic and to any referral facility. A copy of this summary will also be filed in the subject's chart. Appendix A-7-1.
- The **needle biopsy form** on which will appear the indications for biopsy, when, how, and by whom biopsy was performed, information about the initial evaluation of the sample, and the results of the cytologic examination. This form will be keyed (*at the data coordinating center?*) and later filed in the subject's chart. Appendix A-5-8.
- The **pathology form** will be used to record the pathologic diagnosis of thyroid disease. It will be completed by the study pathologist and sent to the data coordinating center to be keyed. A copy will be filed in the subject's record. Appendix A-8-1.
- The **hospitalization abstract form** will be used to record non-study hospitalizations related to thyroid conditions. This form will be completed by the epidemiology group and reviewed by the study endocrinologist. It will be keyed by the epidemiology group and the data sent to the data coordinating center. The form will be filed in the subject's record. Appendix A-8-2.

- The **death data form** which will provide information of the date and causes of death for a participant who dies during the course of the study. It will be completed by and keyed by staff of the epidemiology group. The form will be filed in the subject's chart. Appendix A-8-3.

9.2.1.1 QUALITY CONTROL FOR STUDY FORMS

Measures will be taken at each step in the handling of study data forms to ensure that the data are of high quality. These measures include:

- Double keying, at least initially, to establish error rates.
- Computer edits for missing forms, for completeness or recorded information, for internal consistency, for consistency with research protocol requirements, and for consistency with other information in the database.
- Independent expert review of form content, e.g., the death data form.

9.2.2 SOFTWARE

Software systems will be developed by the data coordinating center to support the management of the study and the processing of the data collected. The management system will be used to track the participation status of subjects throughout the course of the study. It will indicate whether or not the subject has completed the examination components in a particular year of the study, whether the subject is deceased, whether he is lost to follow-up, etc. The management system will be used to generate progress reports to assist project staff in monitoring the study. Software for processing the study data will include keying, editing and updating components. Computer edits will be used to check the data for internal consistency, completeness, acceptable codes, etc..

The data processing systems utilized for the study will make use of the following software packages:

- MS DOS 6.21
- NetWare 4.1
- MS Windows 95, NT 4.0
- Delphi 2.0 Client-Server
- Oracle(Interbase)

9.3 PROCESSING OF STUDY DATA

Processing study data, that is, data from all the data collection forms and some of the management forms listed in Section 9.2.1, includes manual editing, coding, keying and computer editing. These procedures are detailed in this section.

9.3.1 MANUAL EDIT

Before the data forms are keyed into the computer they must be scanned for completeness, presence of written comments that will require codes, illegible entries, etc. This will be done by the data entry specialist as soon as possible. If problems are found which require it, the form should be returned to the person who completed it for correction. Manual editing should be done relatively quickly; a minimal delay before keying is desirable.

9.3.2 CODING

Coding is the process of assigning a numeric value to a response. To the extent possible, items on the data collection forms will be precoded, that is, they will have numeric codes already assigned on the data form. However, on some forms there may be a few items which require coding after the form is completed. These items include residential information on the interview, diseases and responses in which the answer given does not fit into existing precoded categories. (See Section 9.3.2.2 and 9.3.2.4 below.) Detailed item-by-item coding specifications will be prepared for every data form.

The data entry specialist will be responsible for coding these items. All codes assigned must be documented in a **Coding Decision Log**. Since coding will be done in more than one location and over an extended period of time, it is important that consistent decisions be made within and across the centers about how items are coded. Therefore, the coding decision log will be routed through the Data Coordinating Center for review. Decisions which are reviewed and approved by the Data Coordinating Center must be dated and distributed periodically to every location and entered into the Coding Decision Log for future reference. For consistency, this should be done in such a way that all locations receive the information at the same time.

9.3.2.1 GENERAL CODING GUIDELINES

The following are general guidelines for coding open-ended items and also apply to items in which the respondent has not entered their answer in a pre-existing category and the answer needs to be coded.

- Code the forms in a different color pen from the one used to complete the form (red is suggested).
- Whenever boxes are provided for an entry, the information should be right-justified and any unused boxes on the left filled with zeros (0's). ("Right-justified" means that the last digit of the number to be entered is written in the right-most box.)

Example: if there are 4 boxes available to enter the value '781', the value would be entered as:

0	7	8	1

- Enter one character in each box. Round values after a decimal point to fit in the boxes provided. When rounding off a decimal, use the following rule. If the last digit is between 1 and 4, drop the last digit. If the last digit is between 6 and 9, add one to the preceding digit. Rounding the value "29.3" would give "29," while rounding the value "29.7" would give "30." If the last digit is 5, round up if the preceding digit is odd and round down if the preceding digit is even. Never add boxes. Never add new decimal points. Never move decimal points.

Example: There are 4 boxes, with one box to the right of the decimal point (shown below). The value '385.67' would be entered as:

3	8	5	.	7

Example: There are 4 boxes, without a decimal point. The value '385.67' would be filled is as:

0	3	8	6

- If the value is too large to fit correctly in the boxes provided, fill in the right-most box with an '8' and fill in the rest of the boxes with "9's." Then write the actual value in the right-hand margin of the page.

Example: There are 4 boxes, two to the right of the decimal point. The value '385.67 would be entered as:

9	9	.	9	8

385.67

- Dates - the last two digits of the year go in the last 2 boxes, the number of the month goes in the second 2 boxes, and the number of the day goes in the first 2 boxes.

For example, if the date to be entered is July 17, 1987, the correct way to fill in the date is:

1	7	0	7	8	7

When there is only one digit to go in the 2 boxes that are allowed, that digit goes in the second box and the first box is filled in with a '0'. If any part of the date is unknown, enter '--' in its place to indicate this.

- If an item of information is missing and cannot be obtained, the boxes for that item should be filled with "9's."
- If the item is from a questionnaire and the participant refused to give the information, the boxes for that item should be filled with "9997."

9.3.3 KEYING

Data entry will be done in duplicate by independent data-entry clerks and compared by means of special software. Discrepancies will be resolved by the superviser where the comparison is made. After the data forms have been keyed, the keying verified, and computer edits completed (see below, Section 9.3.4), the forms will be released for filing in the facility where the examination was performed or to which the mobile team is attached. Some forms will be filed at the Central Laboratory or the data coordinating center. The final disposition of each form is provided in Section 9.2.1.

9.3.4 COMPUTER EDITING OF DATA

The keyed data will be edited using specially designed software. Output will be produced which will show items outside acceptable ranges (e.g., a subject who is 80 years old), logically inconsistent (e.g., the subject developed a health condition two years before he was born) and missing. The data entry specialist will be responsible for reviewing this output and determining which items will remain as is and for which data retrieval (requesting information or clarification from the person who completed the form or the study subject himself) will be obtained. Updates will be made when necessary and the data will be continually edited until updating is complete. When correction of a data form is required, a record will be made of the error to document its nature, resolution and the date of resolution.

9.3.4.1 GENERAL EDIT CHECKS

General edit checks will include the following:

- checking for blank fields - if a blank field is not allowed then an error message will be generated
- checking similar data across forms - if discrepancies are found, an error message will be generated

- checking for missing forms
- checking for logical consistency

Valid field edits for all variables are specified in detail in the Data Management Manual.

9.3.4.2 EDIT CONSIDERATIONS-SPECIFIC VARIABLES

The following edit checks apply to specific key variables:

- IDs:
  - check for nonnumeric characters
  - check check digit, if there is one
  - check for duplicate IDs
  - check for nonexistent IDs
- Names:
  - check for nonalphabetic characters
  - check for blank field
- Dates-general:
  - check entire field for non-numeric
  - check that month is greater than 0 and less than 13 and that day is greater than 0 and less than 32
  - check that the day of the month is within valid range for the actual month specified (i.e., 1-28, 1-30, 1-31 and 1-29 in leap year)
- Date of birth:
  - compare it against other dates to make sure it precedes them sufficiently
  - check year to make sure it is within study range
- Date of death:
  - compare it against other dates to make sure it follows all activity (alive) dates
  - check year to make sure it precedes the current date and is within the realm of possibility when there are no birth and/or activity years to check
- Postal code:
  - check for nonalphabetic characters
  - check for blank field

9.4 MONITORING PARTICIPANT STATUS

Throughout the course of the study, the status of participants in the study will be monitored using the Study Management System. This system will be used to track the status of individual participants and to prepare reports to monitor recruitment, enrollment, consent, missing information, completed data collection activities and non-response. Staff of the Examination Center is responsible for entry of some of the information into the system. Listed below are the items of information which will be maintained for each participant in the system. A date will be associated with each status.

- recruitment status
- enrollment status
- informed consent status
- non-response status (includes refused and lost-to-followup)
- screening activities completed
- clinic activities completed
- missing data status
- vital status

The system will allow staff of the examination center to view (and print) information on a particular participant and on its own performance. Study management system data will be transmitted to the Data Coordinating Center where additional management reports will be generated.

9.4.1 REPORTS ON STUDY PROGRESS

The Data Coordinating Center and the Epidemiology are responsible for generating reports for the purposes of monitoring study compliance and study progress. These reports are generally produced monthly, or as needed. The following is list of the standard reports to be generated.

- Participant Schedule of Follow-up Visits
- Summary List of Participant Data
- Edit Check Report
- Summary Report of Data Error Types
- Participant Accrual Report
- Participant Status Report
- Ineligible Participant Report
- Status of Dose Estimation

- Building the Cohort Report

9.4.2 REPORTS ON STUDY FINDINGS

The data coordinating center and the Epidemiology group, together with appropriate professional staff will also be responsible for generating reports of study findings. Some standard and some special reports will be required and needs may change as the study progresses. The following standard reports on study findings are expected initially:

- quarterly report on new nodules
- quarterly report on fine needle biopsy
- quarterly report on new thyroid diagnoses
- quarterly report on initial surgeries
- annual report of second and subsequent surgeries

9.5 QUALITY CONTROL

9.5.1 SECURITY

The security of the data in the main file will be protected by passwords to limit access to authorized personnel. Passwords will be periodically changed to maintain security. In addition, the computers will have surge-protectors to guard against power-surges, and data-entry will be backed up systematically. To guard against catastrophic loss of data, e.g., from fire, there will be a duplicate computer file in a different physical location. Finally, all computers and all incoming diskettes will be routinely checked for computer viruses by appropriate programs designed for the purpose.

9.5.2 BACKUPS

Systems will be developed for backing up data at the local examination centers and at the Data Coordinating Center. These procedures are detailed in the Data Management Manual. Also included is information on recovery procedures in case of data loss.

9.5.3 INDIVIDUAL RECORDS

As noted above, each individual data form will be subjected to scanning for completeness, legibility, etc. and double-keyed. Software will be designed for reviewing the logical consistency of the data, the allowable range of numerical entries, and the presence of impossible codes.

9.5.4 STATISTICAL ANALYSIS

The accumulating data will be statistically analyzed periodically for "drift" or systematic change over time, for consistency among examiners and their equipment, for logical consistency, for patient compliance, and for workload characteristics. In addition, there will be statistical analyses of laboratory results obtained with control samples, and of inter-laboratory results obtained with the same specimens.

This version of Operation Manual is identical as to its content in Russian and English translations.

Agreed:

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